```
$%^Dialog;HighlightOn=%%%;HighlightOff=%%%;

Logging in to Dialog

Trying 31060000009999...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
********
ENTER PASSWORD:
********
Welcome to DIALOG

Dialog level 02.14.01D

Last logoff:  24may03 12:46:32
Logon file405 25may03 10:34:20
        *** ANNOUNCEMENT ***
                ***
--File 581 - The 2003 annual reload of Population Demographics is
complete. Please see Help News581 for details.

                ***
--File 990 - NewsRoom now contains February 2003 to current records.
File 992 - NewsRoom 2003 archive has been newly created and contains
records from January 2003. The oldest months's records roll out of
File 990 and into File 992 on the first weekend of each month.
To search all 2003 records BEGIN 990, 992, or B NEWS2003, a new
OneSearch category.
                ***
--Connect Time joins DialUnits as pricing options on Dialog.
See HELP CONNECT for information.
                ***
--CLAIMS/US Patents (Files 340,341, 942) have been enhanced
with both application and grant publication level in a
single record. See HELP NEWS 340 for information.
                ***
--SourceOne patents are now delivered to your email inbox
as PDF replacing TIFF delivery. See HELP SOURCE1 for more
information.
                ***
--Important news for public and academic
libraries.  See HELP LIBRARY for more information.
                ***
--Important Notice to Freelance Authors--
See HELP FREELANCE for more information
                ***
NEW FILES RELEASED
***World News Connection (File 985)
***Dialog NewsRoom - 2003 Archive (File 992)
***TRADEMARKSCAN-Czech Republic (File 680)
***TRADEMARKSCAN-Hungary (File 681)
***TRADEMARKSCAN-Poland  (File 682)
                ***
UPDATING RESUMED
                ***
RELOADED
***Population Demographics -(File 581)
***CLAIMS Citation (Files 220-222)
REMOVED
***U.S. Patents Fulltext 1980-1989 (File 653)

    >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
    >>>    of new databases, price changes, etc.      <<<
                ****
* * * * See HELP NEWS 225 for information on new search prefixes
and display codes

***                             ***

SYSTEM:HOME
Cost is in DialUnits
Menu System II: D2 version 1.7.8 term=ASCII
                *** DIALOG HOMEBASE(SM) Main Menu ***

 Information:
  1. Announcements (new files, reloads, etc.)
  2. Database, Rates, & Command Descriptions
  3. Help in Choosing Databases for Your Topic
  4. Customer Services (telephone assistance, training, seminars, etc.)
  5. Product Descriptions

 Connections:
  6. DIALOG(R) Document Delivery
  7. Data Star(R)

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      /H = Help          /L = Logoff          /NOMENU = Command Mode

Enter an option number to view information or to connect to an online
 service.  Enter a BEGIN command plus a file number to search a database
(e.g., B1 for ERIC).
? dialog
>>Invalid Option Number

                *** DIALOG HOMEBASE(SM) Main Menu ***

 Information:
  1. Announcements (new files, reloads, etc.)
  2. Database, Rates, & Command Descriptions
  3. Help in Choosing Databases for Your Topic
  4. Customer Services (telephone assistance, training, seminars, etc.)
  5. Product Descriptions

 Connections:
  6. DIALOG(R) Document Delivery
  7. Data Star(R)

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      /H = Help          /L = Logoff          /NOMENU = Command Mode

Enter an option number to view information or to connect to an online
 service.  Enter a BEGIN command plus a file number to search a database
(e.g., B1 for ERIC).
? b 410

      25may03 10:34:23 User226352 Session D700.1
         $0.00    0.159 DialUnits FileHomeBase
    $0.00  Estimated cost FileHomeBase
    $0.00  Estimated cost this search
    $0.00  Estimated total session cost   0.159 DialUnits

File 410:Chronolog(R)  1981-2003/Mar
      (c) 2003 The Dialog Corporation

     Set  Items  Description
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? set hi %%%;set hi %%%
HILIGHT set on as '%%%'%%%
%%%HILIGHT set on as '%%%'
? b biochem
      25may03 10:34:27 User226352 Session D700.2
         $0.00    0.070 DialUnits File410
    $0.00  Estimated cost File410
    $0.01  TELNET
    $0.01  Estimated cost this search
    $0.01  Estimated total session cost   0.228 DialUnits

SYSTEM:OS  - DIALOG OneSearch
  File   5:Biosis Previews(R)  1969-2003/May W3
       (c) 2003 BIOSIS
*File   5: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File   6:NTIS  1964-2003/May W4
       (c) 2003 NTIS, Intl Cpyrght All Rights Res
*File   6: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File  34:SciSearch(R) Cited Ref Sci  1990-2003/May W3
       (c) 2003 Inst for Sci Info
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*File  34: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File  40:Enviroline(R) 1975-2003/May
  File  50:CAB Abstracts 1972-2003/Apr
        (c) 2003 CAB International
*File  50: Truncating CC codes is recommended for full retrieval.
See Help News50 for details.
  File  65:Inside Conferences 1993-2003/May W3
        (c) 2003 BLDSC all rts. reserv.
  File  71:ELSEVIER BIOBASE 1994-2003/May W3
        (c) 2003 Elsevier Science B.V.
  File  73:EMBASE 1974-2003/May W3
        (c) 2003 Elsevier Science B.V.
*File  73: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.
  File  94:JICST-EPlus 1985-2003/May W3
        (c)2003 Japan Science and Tech Corp(JST)
  File  98:General Sci Abs/Full-Text 1984-2003/Apr
        (c) 2003 The HW Wilson Co.
  File 103:Energy SciTec 1974-2003/May B1
        (c) 2003 Contains copyrighted material
*File 103: For access restrictions see Help Restrict.
  File 143:Biol. & Agric. Index 1983-2003/Apr
        (c) 2003 The HW Wilson Co
  File 144:Pascal 1973-2003/May W2
        (c) 2003 INIST/CNRS
  File 155:MEDLINE(R) 1966-2003/May W3
        (c) format only 2003 The Dialog Corp.
*File 155: Medline has been reloaded and accession numbers have
changed.  Please see HELP NEWS 155.
  File 156:ToxFile 1965-2003/May W3
        (c) format only 2003 The Dialog Corporation
*File 156: TOXLINE Special data is now available. See Help News156.
  File 162:Global Health 1983-2003/Apr
        (c) 2003 CAB International
*File 162: Effective May 1, name changes from CAB Health
to Global Health.
  File 172:EMBASE Alert 2003/May W3
        (c) 2003 Elsevier Science B.V.
  File 305:Analytical Abstracts 1980-2003/Apr W4
        (c) 2003 Royal Soc Chemistry
*File 305: Alert feature enhanced for multiple files, duplicate
removal, customized scheduling.  See HELP ALERT.
  File 369:New Scientist 1994-2003/May W2
        (c) 2003 Reed Business Information Ltd.
  File 370:Science 1996-1999/Jul W3
        (c) 1999 AAAS
*File 370: This file is closed (no updates). Use File 47 for more current
information.
  File 399:CA SEARCH(R) 1967-2003/UD=13821
        (c) 2003 American Chemical Society
*File 399: Use is subject to the terms of your user/customer agreement.
Alert feature enhanced for multiple files, etc. See HELP ALERT.
  File 434:SciSearch(R) Cited Ref Sci 1974-1989/Dec
        (c) 1998 Inst for Sci Info

      Set  Items  Description
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? s heart and (diseas? or failure?) and phospholamban
Processing
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Processed  10 of  22 files ...
Processing
Processing
Processed  20 of  22 files ...
Completed processing all files
       2864830  HEART
      14298887  DISEAS?
       1737215  FAILURE?
          6858  PHOSPHOLAMBAN
     S1   1736  HEART AND (DISEAS? OR FAILURE?) AND
PHOSPHOLAMBAN
? rd s1
...examined 50 records  (50)
...examined 50 records  (100)
...examined 50 records  (150)
...examined 50 records  (200)
...examined 50 records  (250)
...examined 50 records  (300)
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...examined 50 records  (1050)
...examined 50 records  (1100)
...examined 50 records  (1150)
...examined 50 records  (1200)
...examined 50 records  (1250)
>>>Record 144:15481845 ignored; incomplete bibliographic data, not retained
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...examined 50 records  (1300)
...examined 50 records  (1350)
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...examined 50 records  (1450)
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...examined 50 records  (1550)
...examined 50 records  (1600)
...examined 50 records  (1650)
...examined 50 records  (1700)
...completed examining records
     S2    927  RD S1 (unique items)
? s s2 and py<2000
Processing
Processing
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Processed  10 of  22 files ...
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Processing
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Completed processing all files
         927  S2
      100969173  PY<2000
     S3    518  S2 AND PY<2000
? s s3 and (treat? or ameloriat?)
Processing
Processed  10 of  22 files ...
Processing
Processed  20 of  22 files ...
Processing
Completed processing all files
         518  S3
      11837445  TREAT?
          79  AMELORIAT?
     S4    72  S3 AND (TREAT? OR AMELORIAT?)
? t s4/7/all
>>>Format 7 is not valid in file 143

 4/7/1    (Item 1 from file: 5)
DIALOG(R)File  5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

12258730  BIOSIS NO.: 200000012232
Elevated levels of endogenous adenosine alter metabolism and enhance
 reduction in contractile function during low-flow ischemia: Associated
 changes in expression of Ca2+-ATPase and %%%phospholamban%%%.
AUTHOR: Sommerschild Hilchen T(a); Lunde Per Kristian; Deindl Elisabeth;
 Jynge Per; Ilebekk Arnfinn; Kirkeboen Knut Arvid
AUTHOR ADDRESS: (a)Institute for Experimental Medical Research,
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Ulleval
Hospital, N-0407, Oslo**Norway
JOURNAL: Journal of Molecular and Cellular Cardiology 31 (10):p1897-1911 Oct., %%%1999%%%
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Adenosine has several potentially cardioprotective effects including vasodilatation, reduction in %%%heart%%% rate and alterations in metabolism. Adenosine inhibits catecholamine-induced increase in contractile function mainly through inhibition of phosphorylation of %%%phospholamban%%% (PLB), the main regulatory protein of Ca2+-ATPase in sarcoplasmic reticulum (SR), and during ischemia it reduces calcium (Ca2+) overload. In this study we examined the effects of endogenous adenosine on contractile function and metabolism during low-flow ischemia (LFI) and investigated whether endogenous adenosine can alter expression of the Ca2+-ATPase/PLB-system and other Ca2+-regulatory proteins. Isolated blood-perfused piglet hearts underwent 120 min 10% flow. Hearts were %%%treated%%% with either saline, the adenosine receptor blocker (8)-sulfophenyl theophylline (8SPT, 300 mumol/l) or the nucleoside transport inhibitor draflazine (1 mumol/l). During LFI, 8SPT did not substantially influence metabolic or fun ctional responses. However, draflazine enhanced the reduction in %%%heart%%% rate, contractile force and MVO2, with less release of H+ and CO2. Before LFI there were no significant differences between groups for any of the proteins (Ca2+-ATPase, ryanodine-receptor, Na+/K+-ATPase) or mRNAs (Ca2+-ATPase, PLB, calsequestrin, Na+/Ca2+-exchanger) measured. At end of LFI mRNA-level of PLB was higher in draflazine-%%%treated%%% hearts compared to both other groups (P<0.01 vs both). Also, at end of LFI protein-level of Ca2+-ATPase was lower in draflazine-%%%treated%%% hearts (P<0.05 vs both), and a parallel trend towards a lower mRNA-level was seen (P=0.11 vs saline and P=0.43 vs 8SPT). During LFI tissue Ca2+ tended to rise in saline- and 8SPT-%%%treated%%% hearts but not in draflazine-%%%treated%%% hearts (at end of LFI, P = 0.01 vs 8SPT). We conclude that the amount of adenosine normally produced during LFI does not substantially influence function and metabolism. However, increased endogenous levels by draflazine enhance downregulation of function and reduce signs of anaerobic metabolism. At end of LFI associated changes in expression of PLB and Ca2+-ATPase were seen. The functional significance was not determined in the present study. However, altered protein-levels might influence Ca2+-handling in sarcoplasmic reticulum and thus affect contractile force and tolerance to ischemia.

4/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12199975 BIOSIS NO.: 199900494824
Status of Ca2+/calmodulin protein kinase phosphorylation of cardiac SR proteins in ischemia-reperfusion.
AUTHOR: Netticadan Thomas; Temsah Rana; Osada Mitsuru; Dhalla Naranjan S(a)
AUTHOR ADDRESS: (a)Inst. of Cardiovascular Sciences, St. Boniface General Hospital Research Centre, 351 Tache Ave., Winnipeg, MB, R2H 2A6**Canada
JOURNAL: American Journal of Physiology 277 (3 PART 1):pC384-C391 Sept., %%%1999%%%
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Although the sarcoplasmic reticulum (SR) is known to regulate the intracellular concentration of Ca2+ and the SR function has been shown to become abnormal during ischemia-reperfusion in the %%%heart%%%, the mechanisms for this defect are not fully understood. Because phosphorylation of SR proteins plays a crucial role in the regulation of SR function, we investigated the status of endogenous Ca2+/calmodulin-dependent protein kinase (CaMK) and exogenous cAMP-dependent protein kinase (PKA) phosphorylation of the SR proteins in control, ischemic (I), and ischemia-reperfused (I/R) hearts %%%treated%%% or not %%%treated%%% with superoxide dismutase (SOD) plus catalase (CAT). SR and cytosolic fractions were isolated from control, I, and I/R hearts %%%treated%%% or not %%%treated%%% with SOD plus CAT, and the SR protein phosphorylation by CaMK and PKA, the CaMK- and PKA-stimulated Ca2+ uptake, and the CaMK, PKA, and phosphatase activities were studied. The SR CaMK and CaMK-stimulated Ca2+ uptake activities, as well as CaMK phosphorylation of Ca2+ pump ATPase (SERCA2a) and %%%phospholamban%%% (PLB), were significantly decreased in both I and I/R hearts. The PKA phosphorylation of PLB and PKA-stimulated Ca2+ uptake were reduced significantly in the I/R hearts only. Cytosolic CaMK and PKA activities were unaltered, whereas SR phosphatase activity in the I and I/R hearts was depressed. SOD plus CAT %%%treatment%%% prevented the observed alterations in SR CaMK and phosphatase activities, CaMK and PKA phosphorylations, and CaMK- and PKA-stimulated Ca2+ uptake. These results indicate that depressed CaMK phosphorylation and CaMK-stimulated Ca2+ uptake in I/R hearts may be due to a depression in the SR CaMK activity. Furthermore, prevention of the I/R-induced alterations in SR protein phosphorylation by SOD plus CAT %%%treatment%%% is consistent with the role of oxidative stress during ischemia-reperfusion injury in the %%%heart%%%.

4/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12199676 BIOSIS NO.: 199900494525
Calcium regulatory proteins and their alteration by transgenic approaches.
AUTHOR: Dillmann W H(a)
AUTHOR ADDRESS: (a)Endocrinology and Metabolism, University of California San Diego, 9500 Gilman Drive (BSB 1 5063), La Jolla, CA, 92093-0618**USA
JOURNAL: American Journal of Cardiology 83 (12A):p89H-91H June 17, %%%1999%%%
ISSN: 0002-9149
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Abnormalities in calcium flux have been linked to abnormal contractile behavior of the %%%heart%%% in patients with congestive %%%heart%%% %%%failure%%% as well as in animal models. Decreased activity or levels of the calcium adenosine triphosphatase of the sarco(endo)plasmic reticulum (SERCA2) particularly have been known to cause a delay in calcium transients. The SERCA2 protein pumps 2 moles of calcium per mole of adenosine triphosphate (ATP) split from the cytoplasm into the sarcoplasmic reticulum, thus lowering the free cytoplasmic calcium concentration. It therefore is of interest to identify mechanisms by which SERCA activity could be increased in the %%%heart%%%. To determine influences of increased expression of the SERCA2 gene on calcium transient and contractile behavior, we constructed transgenic mice and rats expressing a SERCA2 transgene in their %%%heart%%%. In these animals, a 20% increase in SERCA levels occurs due to additional expression of the SERCA transgene. This leads to a corresponding increase in contractile activity as determined by the increase in left ventricular pressure measured as dP/dtmax and decrease in diastolic ventricular

pressure determined as dP/dtmin. Similarly, isolated cardiac myocytes obtained from the %%%heart%%% of transgenic mice showed an accelerated calcium transient and increased speed of shortening and relengthening as determined by edge detection. To determine if SERCA2 transgene expression could have a compensatory effect on the contractile behavior of the %%%heart%%% in transgenic mice expressing SERCA2, these mice were made hypothyroid, and papillary muscle function was determined. Contractile behavior of the papillary muscle of wild-type hypothyroid mice showed a significant increase in muscle relaxation time (RT50). In contrast, SERCA2 transgenic hypothyroid mice showed normal contractile behavior of papillary muscle. A compensatory effect of SERCA transgene expression was therefore demonstrated. In addition, we constructed transgenic rats expressing a SERCA2 transgene in which constriction of the ascending aorta induced cardiac hypertrophy and a delayed contraction of papillary muscle. In preliminary results, we found that SERCA2 transgenic rats submitted to ascending aortic constriction did not show the delayed relaxation of papillary muscle as was found in wild-type rats submitted to aortic constriction. In addition, adenoviral vectors expressing transgenes for calcium-handling proteins can be used to improve cardiac myocyte contraction. Adenoviruses expressing a SERCA transgene or a mutant %%%phospholamban%%% transgene exhibiting dominant negative action were used to infect isolated myocytes %%%treated%%% with a phorbol ester (phorbol 12-myristate 13-acetate), which delays the calcium transients. The calcium transients and contractile behavior of the isolated myocytes indicated that increased SERCA expression or increased expression of mutant %%%phospholamban%%% transgene led to increased SERCA2 activity, resulting in an increased contractile phenotype. Recent findings by other investigators also indicate that decreased SERCA2 activity can be increased under in vivo conditions using adenoviral vector-based SERCA2 expression. A gene therapy type of approach delivering increased amounts of SERCA or %%%phospholamban%%% mutants leading to increased SERCA activity should therefore be considered in the future.

4/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12168324 BIOSIS NO.: 199900463173
Captopril %%%treatment%%% improves the sarcoplasmic reticular Ca2+ transport in %%%heart%%% %%%failure%%% due to myocardial infarction.
AUTHOR: Shao Qiming; Ren Bin; Zarain-Herzberg Angel; Ganguly Pallab K; Dhalla Naranjan S(a)
AUTHOR ADDRESS: (a)Institute of Cardiovascular Sciences, St Boniface General Hospital Research Centre, 351 Tache Avenue, Winnipeg, MB, R2H 2A6 **Canada
JOURNAL: Journal of Molecular and Cellular Cardiology 31 (9):p1663-1672 Sept., %%%1999%%%
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Although captopril, an angiotensin-converting enzyme (ACE) inhibitor, has been shown to exert a beneficial effect on cardiac function in %%%heart%%% %%%failure%%%, its effect on the status of sarcoplasmic reticulum (SR) Ca2+ transport in the failing %%%heart%%% has not been examined previously. In order to determine whether captopril has a protective action on cardiac function, as well as cardiac SR Ca2+-pump activity and gene expression, a rat model of %%%heart%%% %%%failure%%% due to myocardial infarction was employed in this study. Sham operated and infarcted rats were given captopril (2 g/l) in drinking water; this %%%treatment%%% was started at either 3 or 21 days and was carried out until 8 weeks after the surgery. The untreated animals with myocardial infarction showed increased %%%heart%%% weight and elevated left ventricular end diastolic pressure, reduced rates of pressure development and pressure fall, as well as depressed SR Ca2+ uptake and Ca2+-stimulated ATPase activities in comparison with the sham control group. These hemodynamic and biochemical changes in the failing hearts were prevented by %%%treatment%%% of the infarcted animals with captopril. Likewise, the observed reductions in the SR Ca2+ pump and %%%phospholamban%%% protein contents, as well as in the mRNA levels for SR Ca2+ pump ATPase and %%%phospholamban%%%, in the failing %%%heart%%% were attenuated by captopril %%%treatment%%%. These results suggest that %%%heart%%% %%%failure%%% is associated with a defect in the SR Ca2+ handling and a depression in the gene expression of SR proteins; the beneficial effect of captopril in %%%heart%%% %%%failure%%% may be due to its ability to prevent remodeling of the cardiac SR membrane.

4/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12020017 BIOSIS NO.: 199900300536
Minimal amount of insulin can reverse diabetic %%%heart%%% function: Sarcoplasmic reticulum Ca2+ transport and %%%phospholamban%%% protein expression.
AUTHOR: Kim Hae Won(a); Cho Yong Sun; Lee Yun Song; Lee Eun Hee; Lee Hee Ran
AUTHOR ADDRESS: (a)Department of Pharmacology, University of Ulsan College of Medicine, 388-1 Poongnapdong, Songpa-**South Korea
JOURNAL: Korean Journal of Physiology & Pharmacology 3 (2):p175-182 April, %%%1999%%%
ISSN: 1226-4512
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In the present study, the underlying mechanisms for diabetic functional derangement and insulin effect on diabetic cardiomyopathy were investigated with respect to sarcoplasmic reticulum (SR) Ca2+-ATPase and %%%phospholamban%%% at the transcriptional and translational levels. The maximal Ca2+ uptake and the affinity of Ca2+-ATPase for Ca2+ were decreased in streptozotocin-induced diabetic rat cardiac SR, however, even minimal amount of insulin could reverse both parameters. Levels of both mRNA and protein of %%%phospholamban%%% were significantly increased in diabetic rat hearts, whereas the mRNA and protein levels of SR Ca2+-ATPase were significantly decreased. In case of %%%phospholamban%%%, insulin %%%treatment%%% reverses these parameters to normal levels. Minimal amount of insulin could reverse the protein levels; however, it could not reverse the mRNA level of SR Ca2+-ATPase at all. Thus, the decreased SR Ca2+ uptake appear to be largely attributed to the decreased SR Ca2+-ATPase level, which is further impaired due to the inhibition by the increased level of %%%phospholamban%%%. These results indicate that insulin is involved in the control of intracellular Ca2+ in the cardiomyocyte through multiple target proteins via multiple mechanisms for the decrease in the mRNA for both SR Ca2+-ATPase and %%%phospholamban%%% which are unknown and needs further study.

4/7/6 (Item 6 from file: 5)

DIALOG(R)File 5:Biosis Previews(R)

11945373 BIOSIS NO.: 199900191482
Effect of angiotensin-converting enzyme inhibition protein kinase C and SR proteins in %%%heart%%% %%%failure%%%.
AUTHOR: Takeishi Yasuchika; Bhagwat Ajit; Ball Nancy A; Kirkpatrick Darry L
; Periasamy Muthu; Walsh Richard A(a)
AUTHOR ADDRESS: (a)Div. Cardiol., Univ. Cincinnati, Coll. Med., 231 Bethesda, Ave., Rm. 33534, Cincinnati OH 45267-**USA
JOURNAL: American Journal of Physiology 276 (1 PART 2):pH53-H62 Jan., %%%1999%%%
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We tested the hypothesis that activation of protein kinase C (PKC) isoforms in pressure-overload %%%heart%%% %%%failure%%% was prevented by angiotensin-converting enzyme (ACE) inhibition, resulting in normalization of cardiac sarcoplasmic reticulum (SR) Ca2+ ATPase (SERCA) 2a and %%%phospholamban%%% protein levels and improvement in intracellular Ca2+ handling. Aortic banded and control guinea pigs were given ramipril (5 mg cntdot kg-1 cntdot day-1) or placebo for 8 wk. Ramipril-%%%treated%%% banded animals had lower left ventricular (LV) and lung weight, improved survival, increased isovolumic LV mechanics, and improved cardiomyocyte Ca2+ transients compared with placebo-%%%treated%%% banded animals. This was associated with maintenance of SERCA2a and %%%phospholamban%%% protein expression. Translocation of PKC-alpha and epsilon was increased in placebo %%%treated%%% banded guinea pigs compared with controls and was attenuated significantly by %%%treatment%%% with ramipril. We conclude that ACE inhibition attenuates PKC translocation and prevents downregulation of Ca2+ cycling protein expression in pressure-overload hypertrophy. This represents a mechanism for the beneficial effects of this therapy on LV function and survival in %%%heart%%% %%%failure%%%.

4/7/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11937698 BIOSIS NO.: 199900183807
Tumor necrosis factor-alpha decreases the phosphorylation levels of %%%phospholamban%%% and troponin I in spontaneously beating rat neonatal cardiac myocytes.
AUTHOR: Yokoyama Tomoyuki(a); Arai Masashi; Sekiguchi Kenichi; Tanaka Toru; Kanda Tsugiyasu; Suzuki Tadashi; Nagai Ryozo
AUTHOR ADDRESS: (a)Second Dep. Intern. Med., Gunma Univ. Sch. Med., 3-39-22 Showa-machi, Maebashi 371**Japan
JOURNAL: Journal of Molecular and Cellular Cardiology 31 (1):p261-273 Jan., %%%1999%%%
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The tumor necrosis factor (TNF) alpha level is elevated in patients with advanced %%%heart%%% %%%failure%%%, and the phosphorylation of contractile regulatory proteins is reduced in the human %%%heart%%%. We hypothesized that TNFalpha affects the phosphorylation of proteins involved in regulating contraction: %%%phospholamban%%% (PLB), myosin light chain 2 (MLC2) and troponin I (TnI). Spontaneously beating rat neonatal cardiac myocytes, prelabelled with (32P)orthophosphate, were %%%treated%%% with TNFalpha for 30 min, and stimulated with isoproterenol for 5 min. 32P-labelled myofIbrillar proteins were isolated by 15% SDS-PAGE. Baseline phosphorylation levels of PLB, TnI and an unknown 23kDa phosphoprotein were decreased by TNFalpha in a dose-dependent manner. Moreover, TNFalpha attenuated the phosphorylation levels of PLB and TnI increased by a concentration of 0.01 muM isoproterenol, but not by 1 muM of isoproterenol. Although TNFalpha had no effect on the cAMP content or cAMP-dependent protein kinase activity in the presence or absence of isoproterenol, an inverse relationship was observed between the concentration of TNFalpha and the cGMP content in cardiac myocytes, and %%%treatment%%% with TNFalpha resulted in a concentration-dependent increase in type 2A protein phosphatase activity. The observation that TNFalpha decreases phosphorylation levels of PLB and TnI in cardiac myocytes suggests that the reduction of these protein phosphorylation levels is partially responsible for alterations of intracellular Ca2+-cycling and the force of contraction in TNF alpha-%%%treated%%% cardiac myocytes. Furthermore, TNFalpha reduces myocyte contraction and protein phosphorylation states possibly via cAMP-independent mechanisms, at least in part, by the activation of type 2A protein phosphatase.

4/7/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11862554 BIOSIS NO.: 199900108663
Sub-antihypertensive doses of ramipril normalize sarcoplasmic reticulum calcium ATPase expression and function following cardiac hypertrophy in rats.
AUTHOR: Boateng Samuel Y; Seymour Anne-Marie L; Bhutta Nabeela S; Dunn Michael J; Yacoub Magdi H; Boheler Kenneth R(a)
AUTHOR ADDRESS: (a)NIH/NIA/GRC/LCS, 5600 Nathan Shock Drive, Baltimore, MD 21224-6825**USA
JOURNAL: Journal of Molecular and Cellular Cardiology 30 (12):p2683-2694 Dec., %%%1998%%%
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We examined the hypothesis that the angiotensin converting enzyme inhibitor ramipril at sub-antihypertensive concentrations could improve sarcoplasmic reticulum (SR) CaATPase expression and function in compensated hypertrophied rat hearts. Five weeks after abdominal aortic constriction, rats received a daily dose (50 mug/kg/day) of ramipril or vehicle for 4 weeks. Cardiac angiotensin-converting enzyme (ACE) activity increased with cardiac hypertrophy (CH) but returned to normal following ramipril %%%treatment%%%. SR CaATPase protein levels and activity decreased with CH (P<0.05) and were normalized following ramipril %%%treatment%%% (P<0.05 for protein and activity). No change in %%%phospholamban%%% (PLB) protein levels could be demonstrated between any of the groups. In contrast, ramipril %%%treatment%%% specifically increased control SR CaATPase and PLB mRNA levels by >60% (P<0.01) and >30%, respectively. In the hypertrophied group. SR CaATPase increased by 35% (P<0.05 n=6) after ramipril %%%treatment%%%. Calsequestrin mRNA levels were unaffected by ramipril administration. In conclusion, ramipril normalizes SR CaATPase protein expression and function in pressure-overloaded and compensated CH. The effects of ramipril are however multifaceted, affecting RNA and protein expression differentially.

4/7/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11830932 BIOSIS NO.: 199900077041
Dissociation of the effects of forskolin and dibutyryl cAMP on force of contraction and %%%phospholamban%%% phosphorylation in human %%%heart%%% %%%failure%%%.
AUTHOR: Neumann Joachim(a); Bartel Sabine; Eschenhagen Thomas;

Haverich
Axel; Hirt Stefan; Karczewski Peter; Krause Ernst-Georg; Schmitz Wilhelm;
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JOURNAL: Journal of Cardiovascular Pharmacology 33 (1):p157-162 Jan., %%%1999%%%
ISSN: 0160-2446
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Forskolin and dibutyryl cyclic adenosine monophosphate (cAMP) stimulate force of contraction independent of beta-adrenoceptor stimulation. We studied their effects on force of contraction and phosphorylation of regulatory proteins in isolated electrically driven trabeculae carneae from failing human ventricles. The phosphorylation state of the regulatory protein %%%phospholamban%%% was studied because its phosphorylation usually faithfully follows contractility. For comparison, the phosphorylation state of the inhibitory subunit of troponin was studied. The phosphorylation state was inferred from in vitro phosphorylation of homogenates with cAMP-dependent protein kinase in the presence of radioactive gamma(32P)ATP. Proteins were separated by electrophoresis, and radioactivity in the proteins of interest was quantified. The maximal positive inotropic effects occurred at 30 muM forskolin and were attenuated in comparison with the maximal effects to dibutyryl cAMP (1 mM). Both forskolin and dibutyryl cAMP enhanced %%%phospholamban%%% phosphorylation. However, %%%phospholamban%%% phosphorylation in intact trabeculae %%%treated%%% with 30 muM forskolin and 1 mM dibutyryl cAMP was comparable. It is suggested that %%%phospholamban%%% phosphorylation can be dissociated from inotropy at least in isolated trabeculae from failing human hearts.

4/7/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11823227 BIOSIS NO.: 199900069336
Cyclic stretch down-regulates calcium transporter gene expression in neonatal rat ventricular myocytes.
AUTHOR: Cadre Brian M; Qi Ming; Eble Diane M; Shannon Thomas R; Bers Donald M; Samarel Allen M(a)
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JOURNAL: Journal of Molecular and Cellular Cardiology 30 (11):p2247-2259 Nov., %%%1998%%%
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Abnormal intracellular Ca2+ handling in hypertrophied and failing hearts is partly due to changes in Ca2+ transporter gene expression, but the mechanisms responsible for these alterations remain largely unknown. We previously showed that intrinsic mechanical load (i.e. spontaneous contractile activity) induced myocyte hypertrophy, and down-regulated SR Ca2+ ATPase (SERCA2) gene expression in cultured neonatal rat ventricular myocytes (NRVM). In the present study, we examined whether extrinsic mechanical load (i.e. cyclic stretch) also induced NRVM hypertrophy, and led to down-regulation of SERCA2 and other Ca2+ transporter genes which have been associated with cardiac hypertrophy and %%%failure%%% in vivo.
NRVM were maintained in serum-free culture medium under control conditions, or subjected to cyclic mechanical deformation (1.0 Hz, 20% maximal strain, 48 h). Under these conditions, cyclic stretch induced NRVM hypertrophy, as evidenced by significant increases in total protein/DNA ratio, myosin heavy chain (MHC) content, and atrial natriuretic factor (ANF) secretion. Cyclic stretch also induced the MHC isoenzyme "switch" which is characteristic of hemodynamic overload of the rat %%%heart%%% in vivo. Cyclic stretch significantly downregulated SERCA2 and ryanodine receptor (RyR) mRNA and protein levels, while simultaneously increasing ANF mRNA. In contrast, Na+-Ca2+ exchanger and %%%phospholamban%%% mRNA levels were unaffected. Load-dependent SERCA2 and RyR down-regulation was independent of Ca2+ influx via voltage-gated, L-type Ca2+ channels, as cyclic stretch down-regulated SERCA2 and RyR mRNA levels in both control and verapamil-%%%treated%%% NRVM. These results indicate that extrinsic mechanical load (in the absence of other exogenous stimuli) induces NRVM hypertrophy and causes down-regulation of Ca2+ transporter gene expression. This in vitro model system should prove useful to dissect the intracellular signaling pathways responsible for transducing this phenotype during cardiac hypertrophy and %%%heart%%% %%%failure%%% in vivo.

4/7/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11724939 BIOSIS NO.: 199800506670
Molecular aspects of adrenergic signal transduction in cardiac %%%failure%%%.
AUTHOR: Hajjar Roger J; Mueller Frank U; Schmitz Wilhelm; Schnabel Petra;
Boehm Michael(a)
AUTHOR ADDRESS: (a)Univ. Koeln, Klin. III Innere Med., Joseph-Stelzmann-Str. 9, D-50924 Cologne**Germany
JOURNAL: Journal of Molecular Medicine (Berlin) 76 (11):p747-755 Oct., %%%1998%%%
ISSN: 0946-2716
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Abnormal beta-adrenergic signal transduction and intracellular Ca2+ handling appear to be a major cause of systolic and diastolic dysfunction in humans with %%%heart%%% %%%failure%%%. The precise mechanisms which cause an alteration in Ca2+ handling have been a subject of investigation in recent years. Several lines of evidence suggest that activation of neurohormonal systems plays a central role. Altered Ca2+-handling (increased diastolic concentrations, reduced systolic Ca2+ release) have a strong impact on diastolic and systolic performance of failing hearts. Sarcoplasmic reticulum Ca2+ ATPase is reduced in activity and in steady-state mRNA concentration. The Na+-Ca2+ exchanger is upregulated at the mRNA and protein levels. %%%Phospholamban%%% depends strongly on cAMP-dependent phosphorylation. A strong sympathetic activation has been shown to desensitize the cAMP system. At the receptor level, there is downregulation of beta1-adrenergic receptors. An uncoupling of beta2-adrenoceptors has been attributed to an increased activity and gene expression of beta-adrenergic receptor kinase in failing myocardium, leading to phosphorylation and uncoupling of receptors. Finally, recent evidence suggests that cAMP-dependent transcription mechanisms may play a role during beta-adrenergic stimulation and cardiomyopathy with %%%heart%%% %%%failure%%% - by means of altered actions of cAMP response element binding protein, the cAMP response element modulator, or the activating transcription factor 1. The exact characterization of signal transduction defects could offer novel approaches to the pharmacological %%%treatment%%% of %%%heart%%% %%%failure%%%.

4/7/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11626113 BIOSIS NO.: 199800408512
Chronic effects of enalapril and amlodipine on cardiac remodeling in cardiomyopathic hamster hearts.

AUTHOR: Watanabe Masashi; Kawaguchi Hideaki(a); Onozuka Hisao; Mikami Taisei; Urasawa Kazushi; Okamoto Hiroshi; Watanabe Satoshi; Abe Kazuhiro;
Kitabatake Akira
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Kita-ku, Sapporo 060**Japan
JOURNAL: Journal of Cardiovascular Pharmacology 32 (2):p248-259 Aug., %%%1998%%%
ISSN: 0160-2446
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study examined the effects of long-term %%%treatments%%%
with the angiotensin-converting enzyme inhibitor, enalapril, and the calcium antagonist, amlodipine, on the morphologic changes, progressive left ventricular dysfunction, and gene expression of the ryanodine receptor (RyR) and %%%phospholamban%%% (PLN) in dilated cardiomyopathy,
From the ages of 5 through 20 weeks, dilated cardiomyopathic hamsters, B1053.58 (BIO), and control hamsters, F1b, orally received either enalapril or amlodipine. Cardiac function was assessed by echocardiography. At the age of 20 weeks, the collagen volume fractions were analyzed by the stereologic method. RyR and PLN messenger RNAs (mRNAs) were examined by Northern blot in the amlodipine group. In BIO, the reduction of left ventricular percentage of fractional shortening was attenuated in the enalapril group ($p < 0.05$) and amlodipine group ($p < 0.001$), and the increase in the collagen volume fraction and the loss of myocytes were suppressed in the amlodipine group compared with the untreated group. RyR mRNA level decreased in BIO ($p < 0.01$) compared with
F1b, but PLN mRNA level was unchanged. RyR and PLN mRNA levels were unaffected by the %%%treatment%%% with amlodipine. Enalapril and amlodipine prevent progressive remodeling and reduce cardiac dysfunction in BIO. Amlodipine prevents fibrosis and cell death without modifying RyR and PLN mRNA levels in BIO.

4/7/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11439584 BIOSIS NO.: 199800220916
Sarcoplasmic reticulum genes are selectively down-regulated in cardiomyopathy produced by doxorubicin in rabbits.
AUTHOR: Arai Masashi(a); Tomaru Koichi; Takizawa Takako; Sekiguchi Kenichi;
Yokoyama Tomoyuki; Suzuki Tadashi; Nagai Ryozo
AUTHOR ADDRESS: (a)Second Dep. Internal Med., Gunma Univ. Sch. Med., Showa-machi, Maebashi, Gunma 371**Japan
JOURNAL: Journal of Molecular and Cellular Cardiology 30 (2):p243-254 Feb., %%%1998%%%
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The clinical utility of doxorubicin, an antineoplastic agent, is limited by its cardiotoxicity. Our objective was to determine whether expression of genes encoding proteins that affect Ca2+ homeostasis were altered in the hearts of rabbits chronically %%%treated%%% with doxorubicin. Twelve male New Zealand white rabbits received an injection of doxorubicin (2.5 mg/kg i.v.) once a week for 8 weeks. Eight rabbits were similarly injected with saline as controls. The cardiac function of both groups was evaluated 8 weeks after the final injection, as were the levels of expression of mRNA for Ca2+ transport proteins in the sarcoplasmic reticulum and plasma membrane. The amount of the sarcoplasmic reticulum Ca2+-ATPase and the Ca2+ uptake capacity of the protein were also quantitated. Cardiac output was significantly decreased in the doxorubicin-%%%treated%%% group (71+-21 ml/min, $P<0.05$) compared
with the control group (118 +- 15 ml/min). The mRNA levels for the sarcoplasmic reticulum proteins were significantly diminished in the doxorubicin-%%%treated%%% hearts: ryanodine receptor-2 (relative expression level compared with controls, 0.35+-0.13, $P<0.01$), sarcoplasmic reticulum Ca2+-ATPase (0.56+-0.13, $P<0.01$), %%%phospholamban%%% (0.62+-0.20, $P<0.01$) and cardiac calsequestrin (0.57+-0.26, $P<0.01$). In addition, both relative amount of sarcoplasmic reticulum Ca2+-ATPase protein (doxorubicin-%%%treated%%% group, 69 +- 17%
of control, $P<0.01$) and the Ca2+ uptake capacity (46.9 +- 9.8 nmol Ca2+/mg protein-5 min in doxorubicin group v 63.2 +- 10.4 in the control group, $P<0.01$) were concomitantly decreased with its mRNA expression level. Conversely, the mRNA levels for the plasma membrane proteins did not differ from those of control rabbits: the dihydropyridine receptor (relative expression level, 1.03 +- 0.30, N.S.), plasma membrane Ca2+-ATPase (0.93+-0.33, N.S.) and the Na+/Ca2+ exchanger (0.87 +- 0.34, N.S.). These findings suggest that a selective decrease in mRNA expression for sarcoplasmic reticulum Ca2+ transport proteins is responsible for the impaired Ca2+ handling, and thus, for the reduced cardiac function seen in the cardiomyopathy induced in rabbits by the long-term %%%treatment%%% with doxorubicin.

4/7/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11291363 BIOSIS NO.: 199800072695
Injury to the Ca!2!+ ATPase of the sarcoplasmic reticulum in anesthetized dogs contributes to myocardial reperfusion injury.
AUTHOR: Smart Steven C(a); Sagar Kiran B; El Schultz Jo; Warltier David C;
Jones Larry R
AUTHOR ADDRESS: (a)Div. Cardiovascular Med., Dep. Med., Med. Coll. Wisconsin, Milwaukee, WI 53226**USA
JOURNAL: Cardiovascular Research 36 (2):p174-184 Nov., %%%1997%%%
ISSN: 0008-6363
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective: Sarcoplasmic reticulum dysfunction may contribute to
calcium (Ca2+) overload during myocardial reperfusion. The aim of this study was to investigate its role in reperfusion injury. Methods: Open chest dogs undergoing 15 min of left anterior descending coronary artery occlusion and 3 h of reperfusion were randomized to intracoronary infusions of 0.9% saline, vehicle, or the Ca2+ channel antagonist, nifedipine (50 mug/min from 2 minutes before to 5 minutes after reperfusion). After each experiment, transmural myocardial biopsies were removed from ischemic/reperfused and nonischemic myocardium in the beating state and analyzed for (i) sarcoplasmic reticulum protein content (Ca2+ ATPase, %%%phospholamban%%%, and calsequestrin) by immunoblotting
and (ii) Ca2+ uptake by sarcoplasmic reticulum vesicles with and without 300 micromolar ryanodine or the Ca2+ ATPase activator, antiphospholamban
(2D12) antibody. Results: Contractile function did not recover in controls and vehicle-%%%treated%%% dogs after ischemia and reperfusion (mean systolic shortening, -2 +- 2%), but completely recovered in nifedipine-%%%treated%%% dogs (17 +- 2%, $p = NS$ vs. baseline, $p < 0.01$ vs. control). Ventricular fibrillation occurred in 50% of controls and vehicle dogs and 0% of nifedipine-%%%treated%%% dogs ($p < 0.01$). Ca2+ uptake by the sarcoplasmic reticulum vesicles was severely reduced in ischemic/reperfused myocardium of controls and vehicle dogs ($p < 0.01$ vs. nonischemic). Ryanodine and the 2D12 antibody improved, but did not reverse the low Ca2+ uptake. Protein content was similar in ischemic/reperfused and nonischemic myocardium. In contrast, Ca2+ uptake and the responses to ryanodine and 2D12 antibody were normal in ischemic/reperfused myocardium from nifedipine-%%%treated%%% dogs. Conclusion: Dysfunction of the sarcoplasmic reticulum Ca2+ ATPase pump correlates with reperfusion injury. Reactivation of Ca2+ channels at reperfusion contributed to Ca2+ pump dysfunction. Ca2+ pump injury may be
a critical event in myocardial reperfusion injury.

4/7/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11183444 BIOSIS NO.: 199799804589
Thyroid hormone improves function and Ca-2+ handling in pressure overload hypertrophy: Association with increased sarcoplasmic reticulum Ca-2+-ATPase and alpha-myosin heavy chain in rat hearts.
AUTHOR: Chang Kevin C; Figueredo Vincent M; Schreur Joop H M; Kariya Ken-Ichi; Weiner Michael W; Simpson Paul C; Camacho S Albert(a)
AUTHOR ADDRESS: (a)Div. Cardiol., Room 5G1, UCSF/San Francisco Gen. Hosp., San Francisco, CA 94110**USA
JOURNAL: Journal of Clinical Investigation 100 (7):p1742-1749 %%%1997%%%
ISSN: 0021-9738
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We asked whether thyroid hormone (T-4) would improve %%%heart%%% function in left ventricular hypertrophy (LVH) induced by pressure overload (aortic banding). After banding for 10-22 wk, rats were %%%treated%%% with T-4 or saline for 10-14 d. Isovolumic LV pressure and cytosolic (Ca-2+) (indo-1) were assessed in perfused hearts. Sarcoplasmic reticulum Ca-2+ATPase (SERCA), %%%phospholamban%%%, and alpha- and beta-myosin heavy chain (MHC) proteins were assayed in homogenates of myocytes isolated from the same hearts. Of 14 banded hearts %%%treated%%% with saline, 8 had compensated LVH with normal function (LVH-comp), whereas 6 had abnormal contraction, relaxation, and calcium handling (LVH-decomp). In contrast, banded animals %%%treated%%% with T-4 had no myocardial dysfunction; these hearts had increased contractility, and faster relaxation and cytosolic (Ca-2+) decline compared with LVH-comp and LVH-decomp. Myocytes from banded hearts %%%treated%%% with T-4 were hypertrophied but had increased concentrations of alpha-MHC and SERCA proteins, similar to physiological hypertrophy induced by exercise. Thus thyroid hormone improves LV function and calcium handling in pressure overload hypertrophy, and these beneficial effects are related to changes in myocyte gene expression. Induction of physiological hypertrophy by thyroid hormone-like signaling might be a therapeutic strategy for %%%treating%%% cardiac dysfunction in pathological hypertrophy and %%%heart%%% %%%failure%%%.

4/7/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10792836 BIOSIS NO.: 199799413981
Mechanisms of the contractile effects of levosimendan in the mammalian %%%heart%%%.
AUTHOR: Boknik Peter(a); Neumann Joachim; Kaspareit Grit; Schmitz Wilhelm; Scholz Hasso; Vahlensieck Ute; Zimmermann Norbert
AUTHOR ADDRESS: (a)Institut fuer Pharmakologie und Toxikologie der Westfaelischen Wilhelms-Universitaet, Domagkstra**Germany
JOURNAL: Journal of Pharmacology and Experimental Therapeutics 280 (1):p 277-283 %%%1997%%%
ISSN: 0022-3565
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In spontaneously beating guinea pig right atria, levosimendan (LS, or R-((-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl)-hydrazono)propanedinitrile) exerted a positive chronotropic effect starting at 0.1 mu-M. In electrically driven guinea pig left atria, LS (0.1-10 mu-M) increased force of contraction without changing time parameters of contraction. In electrically driven right papillary muscles, LS (0.1-10 mu-M) enhanced force of contraction without affecting time parameters of contraction. The maximal effect on force of contraction at 10 mu-M amounted to 130 +- 8.6% of predrug value. The positive inotropic effect of LS in papillary muscles was greatly diminished by additionally applied carbachol. In (32P)-labeled guinea pig ventricular cardiomyocytes, LS increased the phosphorylation state of %%%phospholamban%%%, the inhibitory subunit of troponin and C-protein. The maximal effect at 1 mu-M amounted to 134 +- 8.6%, 124 +- 4.2% and 121 +- 8% of control for %%%phospholamban%%%, the inhibitory subunit of troponin and C-protein, respectively. LS (1 mu-M) increased cAMP content from 6.3 +- 0.3 to 8.1 +- 0.3 pmol/mg protein in guinea pig ventricular cardiomyocytes. Furthermore, whole-cell patch-clamp studies were performed in guinea pig ventricular cardiomyocytes. In this setup, 10 mu-M LS increased the amplitude of L-type Ca++ current to 402 +- 86% of predrug value.

4/7/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10754053 BIOSIS NO.: 199799375198
Alterations in inotropy, nitric oxide and cyclic GMP synthesis, protein phosphorylation and ADP-ribosylation in the endotoxin-%%%treated%%% rat myocardium and cardiomyocytes.
AUTHOR: Sulakhe Prakash V(a); Sandirasegarane Lakshman; Davis J Paul; Vo Xuan T; Costain Williard; Mainra Rahul R
AUTHOR ADDRESS: (a)Dep. Physiology, Coll. Med., 107 Wiggins Road, Univ. Saskatchewan, Saskatoon, S7N 5E5**Canada
JOURNAL: Molecular and Cellular Biochemistry 163-164 (0):p305-318 %%%1996%%%
ISSN: 0300-8177
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To evaluate the effects of the in vivo endotoxin %%%treatment%%% of the rat on (1) the contractile responses in the subsequently isolated papillary muscle to adrenergic and cholinergic agonists and (2) the biochemical parameters (cyclic GMP, nitric oxide synthesis, protein phosphorylation and ADP-ribosylation) in the subsequently isolated cardiomyocytes. Following the in vivo endotoxin %%%treatment%%% (4 mg/kg i.p., 18 h), contractile responses to increasing amounts of isoprenaline or to increasing amounts of oxotremorine in the presence of a fixed amount of isoprenaline were determined in isolated papillary strips. Activities of nitric oxide synthase, guanylyl cyclase, as well as phosphorylation of %%%phospholamban%%% and troponin-inhibitory subunit, and pertussis toxin-catalyzed and endogenous ADP-ribosylations were determined in the intact cardiomyocytes and subcellular fractions. The increase in the force of contraction by isoprenaline was reduced, while its inhibition by oxotremorine was greater in the endotoxin-%%%treated%%% papillary strips. The activities of both nitric oxide synthase, primarily of the inducible form of the enzyme, and cytosolic guanylyl cyclase were higher while the phosphorylations of both %%%phospholamban%%% and troponin-inhibitory subunit were of lesser magnitude in the cardiomyocytes following the in vivo endotoxin %%%treatment%%%. Pertussis toxin-catalyzed ADP-ribosylation of the 41 kDa polypeptide, which is the alpha subunit of Gi, was also decreased. The results of the present study support the postulate that alterations in both the cyclic AMP and cyclic GMP signalling cascade contribute to the myocardial dysfunction caused by endotoxin and cytokines.

4/7/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10614882 BIOSIS NO.: 199699236027
Modification of sarcoplasmic reticulum gene expression in pressure overload cardiac hypertrophy by etomoxir.
AUTHOR: Zarain-Herzberg Angel; Rupp Heinz; Elimban Vijayan; Dhalla Naranjan S(a)
AUTHOR ADDRESS: (a)Div. Cardiovascular Sci., St. Boniface General Hosp. Res. Cent., 351 Tache Ave., Winnipeg, Manit**Canada

JOURNAL: FASEB Journal 10 (11):p1303-1309 %%%1996%%%
ISSN: 0892-6638
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Pressure overload on the %%%heart%%% is known to produce hypertrophy of cardiomyocytes and distinct changes in protein phenotype, including reduced expression of the gene for the sarcoplasmic reticulum (SR) Ca-2+ ATPase (SERCA2). In this study we have shown that the decrease in SERCA2 gene expression (normalized by poly(A)+ mRNA or 18 S rRNA) in rats with 8 wk of aortic constriction was prevented by %%%treatment%%% with etomoxir, an inhibitor of carnitine palmitoyltransferase 1. The reduction in steady-state mRNA levels for SR %%%phospholamban%%% (PLP) and Ca-2+ release channel (CRC) in the pressure-overloaded animals was also prevented without any reduction in the extent of cardiac hypertrophy by %%%treatment%%% with etomoxir. Although no changes in mRNA levels for GAPDH were evident in rats with pressure overload, the expression of the alpha-skeletal actin was increased; this change was prevented by etomoxir. Similar beneficial effects of etomoxir %%%treatment%%% were also evident when the gene expression for SR SERCA2, PLP, and CRC in the hypertrophied %%%heart%%% was normalized with respect to mRNA for GAPDH. These results support the view that drugs such as etomoxir may increase the abundance of the mRNA for SR proteins in the hypertrophied %%%heart%%% and thus may prevent the transition of cardiac hypertrophy into %%%heart%%% %%%failure%%%.

4/7/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10284549 BIOSIS NO.: 199698739467
Arterial delivery of genetically labelled skeletal myoblasts to the murine %%%heart%%%: Long-term survival and phenotypic modification of implanted myoblasts.
AUTHOR: Robinson Shawn W; Cho Peter W; Levitsky Hyam I; Olson Jean J; Hruban Ralph H; Acker Michael A; Kessler Paul D(a)
AUTHOR ADDRESS: (a)Johns Hopkins Univ. Sch. Med., Ross Res. Room 812, 720 Rutland Ave., Baltimore, MD 21205**USA
JOURNAL: Cell Transplantation 5 (1):p77-91 %%%1996%%%
ISSN: 0963-6897
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The ability to replace damaged myocardial tissue with new striated muscle would constitute a major advance in the %%%treatment%%% of %%%diseases%%% that irreversibly injure cardiac muscle cells. The creation of focal grafts of skeletal muscle has been reported following the intramural injection of skeletal myoblasts into both normal and injured myocardium. The goals of this study were to determine whether skeletal myoblast-derived cells can be engrafted into the murine %%%heart%%% following arterial delivery. The murine %%%heart%%% was seeded with genetically labeled C2C12 myoblasts introduced into the arterial circulation of the %%%heart%%% via a transventricular injection. A transventricular injection provided access to the coronary and systemic circulations. Implanted cells were characterized using histochemical staining for beta-galactosidase, immunofluorescent staining for muscle-specific antigens, and electron microscopy. Initially the injected cells were observed entrapped in myocardial capillaries. One week after injection myoblasts were present in the myocardial interstitium and were largely absent from the myocardial capillary bed. Implanted cells underwent myogenic development, characterized by the expression of a fast-twitch skeletal muscle sarcoplasmic reticulum calcium ATPase (SERCA1) and formation of myofilaments. Four months following injection myoblast-derived cells began to express a slow-twitch/cardiac protein, %%%phospholamban%%%, that is normally not expressed by C2C12 cells in vitro. Most surprisingly, regions of close apposition between LacZ labeled ells and native cardiomyocytes contained structures that resembled demosomes, fascia adherens junctions, and gap junctions. The cardiac gap junction protein, connexin43, was localized to some of the interfaces between implanted cells and cardiomyocytes. Collectively, these findings suggest that arterially delivered myoblasts can be engrafted into the %%%heart%%%, and that prolonged residence in the myocardium may alter the phenotypes of these skeletal muscle-derived cells. Furhter studies are necessary to determine whether arterial delivery of skeletal myoblasts can be developed as %%%treatment%%% for myocardial dysfunction.

4/7/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09900979 BIOSIS NO.: 199598355897
Differential influences of carnitine palmitoyltransferase-1 inhibition and hyperthyroidism on cardiac growth and sarcoplasmic reticulum phosphorylation.
AUTHOR: Vetter R(a); Kott M; Rupp H
AUTHOR ADDRESS: (a)Max-Delbrueck-Centrum Molekulare Medizin, Robert-Roessle-Strasse 10, 13122 Berlin-Buch**Germany
JOURNAL: European Heart Journal 16 (SUPPL. C):p15-19 %%%1995%%%
ISSN: 0195-668X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To characterize interventions resulting in 'physiological' growth of the %%%heart%%%, Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR) had hyperthyroidism induced (0.05 mg cntdot kg-1 cntdot day-1 triiodothyronine for 6 days) or were %%%treated%%% with a high dose of the carnitine palmitoyltransferase-1 inhibitor, etomoxir (15 mg cntdot kg-1 cntdot day-1 for 5 weeks). Etomoxir increased cardiac growth evenly, but hyperthyroidism resulted in an over-proportional higher right ventricular weight. Both interventions increased the proportion of the myosin isozyme V-1. The rate of sarcoplasmic reticulum (SR) Ca-2+ uptake was increased to a greater extent in hyperthyroid rats than in etomoxir-%%%treated%%% rats (P lt 0.05). Left ventricular levels of immunoreactivephospholamban (semiquantitative ELISA) were moderately decreased (P lt 0.05) in hyperthyroid rats but not in etomoxir-%%%treated%%% rats. The protein kinase A-catalyzed in vitro 32P-incorporation into the SR Ca-2+ pump modulator %%%phospholamban%%% was greatly reduced (P lt 0.05) in hyperthyroid rats, indicating an increased in vivo phosphorylation. Etomoxir did not affect %%%phospholamban%%% phosphorylation in WKY rats. Thus, both a higher in vivo %%%phospholamban%%% phosphorylation state and a greater number of active Ca-2+ pumps contributed to an increased rate of SR Ca-2+ uptake in hyperthyroidism. The etomoxir %%%treatment%%% primarily increased the number of active Ca-2+ pumps. A scheme is proposed focusing on long-term vs short-term regulation of the SR Ca-2+ pump/%%%phospholamban%%% system in %%%diseased%%% states.

4/7/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09756564 BIOSIS NO.: 199598211482
Cardiac contractile responses to cantharidin in isoproterenol %%%treated%%% rats.
AUTHOR: Linck B; Boknik P; Knapp J; Mueller F U; Neumann J; Schmitz W; Sickler H; Vahlensieck U
AUTHOR ADDRESS: Inst. Pharmakol. und Toxicol. der Univ., Domagkstr. 12, D-48129 Muenster**Germany

JOURNAL: FASEB Journal 9 (4):pA932 %%%1995%%%
CONFERENCE/MEETING: Experimental Biology 95, Part II Atlanta, Georgia, USA
April 9-13, 1995
ISSN: 0892-6638
RECORD TYPE: Citation
LANGUAGE: English

4/7/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06692108 BIOSIS NO.: 000088001525
REGULATION OF MYOCARDIAL CALCIUM ATPASE AND %%%PHOSPHOLAMBAN%%% MESSENGER RNA EXPRESSION IN RESPONSE TO PRESSURE OVERLOAD AND THYROID HORMONE
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JOURNAL: PROC NATL ACAD SCI U S A 86 (8). 1989. 2966-2970. %%%1989%%%
FULL JOURNAL NAME: Proceedings of the National Academy of Sciences of the United States of America
CODEN: PNASA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The sarcoplasmic reticulum (SR) and the contractile protein myosin play an important role in myocardial performance. Both of these systems exhibit plasticity.sbd.i.e., quantitative and/or qualitative reorganization during development and in response to stress. Recent studies indicate that SR Ca2+ uptake function is altered in adaptive cardiac hypertrophy and %%%failure%%%. The molecular basis (genetic and phenotypic) for these changes is not understood. In an effort to determine the underlying causes of these changes, we characterized the rabbit cardiac Ca2+-ATPase phenotype by molecular cloning and ribonuclease A mapping analysis. Our results show that the %%%heart%%% muscle expresses only the slow-twitch SR Ca2+-ATPase isoform. Second, we quantitated the steady-state mRNA levels of two major SR Ca2+ regulatory proteins, the Ca2+-ATPase and %%%phospholamban%%%, to see whether changes in mRNA content might provide insight into the basis for functional modification in the SR of hypertrophied hearts. In response to pressure overload hypertrophy, the relative level of the slow-twitch/cardiac SR C2+-ATPase mRNA was decreased to 34% of control at 1 week. The relative Ca2+-ATPase mRNA level increased to 167% of contrll after 3 days of %%%treatment%%% with thyroid hormone. In contrast, in hypothyroid animals, the relative Ca2+-ATPase mRNA level decreased to 51% of control at 2 weeks. The relative level of %%%phospholamban%%% mRNA was decreased in 36% in 1-week pressure overload. Hyperthyroidism induced a decrease to 61% in the %%%phospholamban%%% mRNA level after 3 days of %%%treatment%%% , while hypothyroidism had virtually no effect on %%%phospholamban%%% mRNA levels. These data indicate that the expression of SR Ca2+-ATPase and %%%phospholamban%%% mRNA may not be coordinately regulated during myocardial adaptation to different physiological conditions.

4/7/23 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

08255099 Genuine Article#: 263LM Number of References: 19
Title: Restoration of contractile function in isolated cardiomyocytes from failing human hearts by gene transfer of SERCA2a
Author(s): delMonte F; Harding SE; Schmidt U; Matsui T; Kang ZB; Dec W; Gwathmey JK; Rosenzweig A; Hajjar RJ (REPRINT)
Corporate Source: HARVARD UNIV,MASSACHUSETTS GEN HOSP, SCH MED, CARDIOVASC RES CTR, 149 13TH ST, CNY 4/BOSTON//MA/02129 (REPRINT); HARVARD UNIV,MASSACHUSETTS GEN HOSP, SCH MED, CARDIOVASC RES CTR/BOSTON//MA/02129; HARVARD UNIV,MASSACHUSETTS GEN HOSP, SCH MED, HEART FAILURE & CARDIAC TRANSPLANTAT CTR/BOSTON//MA/02129; BOSTON UNIV,SCH MED/BOSTON//MA/02118; UNIV LONDON IMPERIAL COLL SCI TECHNOL & MED,/LONDON//ENGLAND/
Journal: CIRCULATION, %%%1999%%%, V100, N23 (DEC 7), P2308-2311
ISSN: 0009-7322 Publication date: 19991207
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106
Language: English Document Type: ARTICLE
Abstract: Background-Failing human myocardium is characterized by abnormal relaxation, a deficient sarcoplasmic reticulum (SR) Ca2+ uptake, and a negative frequency response, which have all been related to a deficiency in the SR Ca2+ ATPase (SERCA2a) pump.

Methods and Results-To test the hypothesis that an increase in SERCA2a could improve contractile function in cardiomyocytes, we overexpressed SERCA2a in human ventricular myocytes from 10 patients with end-stage %%%heart%%% %%%failure%%% and examined intracellular Ca2+ handling and contractile function. Overexpression of SERCA2a resulted in an increase in both protein expression and pump activity and induced a faster contraction velocity (26.7 +/- 6.7% versus 16.6 +/- 2.7% shortening per second, P < 0.005) and enhanced relaxation velocity (32.0 +/- 10.1% versus 15.1 +/- 2.4%, P < 0.005). Diastolic Ca2+ was decreased in failing cardiomyocytes overexpressing SERCA2a (270 +/- 26 versus 347 +/- 30 nmol/L, P < 0.005), whereas systolic Ca2+ was increased (601 +/- 38 versus 508 +/- 25 nmol/L, P < 0.05), In addition, the frequency response was normalized in cardiomyocytes overexpressing SERCA2a.

Conclusions-These results support the premise that gene-based therapies and targeting of specific pathways in human %%%heart%%% %%%failure%%% may offer a new modality for the %%%treatment%%% of this %%%disease%%%.

4/7/24 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

07592572 Genuine Article#: 186EK Number of References: 34
Title: Serial changes in sarcoplasmic reticulum gene expression in volume-overloaded cardiac hypertrophy in the rat: effect of an angiotensin II receptor antagonist
Author(s): Hashida H; Hamada M (REPRINT) ; Hiwada K
Corporate Source: EHIME UNIV,SCH MED, DEPT INTERNAL MED 2/SHIGENOBU/EHIME 7910295/JAPAN/ (REPRINT); EHIME UNIV,SCH MED, DEPT INTERNAL MED 2/SHIGENOBU/EHIME 7910295/JAPAN/
Journal: CLINICAL SCIENCE, %%%1999%%%, V96, N4 (APR), P387-395
ISSN: 0143-5221 Publication date: 19990400
Publisher: PORTLAND PRESS, 59 PORTLAND PLACE, LONDON W1N 3AJ, ENGLAND
Language: English Document Type: ARTICLE
Abstract: This study was designed to clarify whether gene expression in the card iac sarcoplasmic reticulum [sarcoplasmic reticulum Ca2+-ATPase (SERCA), %%%phospholamban%%%, ryanodine receptor and calsequestrin] changes in accordance with left ventricular functional alterations in the volume-overloaded %%%heart%%%. Further, the effect of the angiotensin II type I receptor antagonist, TCV-116, on the expression of these genes was also evaluated. Left ventricular fractional shortening was significantly increased at 7 days, had returned to

control levels at 21 days, and had significantly decreased at 35 days after the shunt operation, compared with sham-operated rats. The level of SERCA mRNA was significantly decreased at both 21 days and 35 days after the shunt operation. The levels of ryanodine receptor and %%%phospholamban%%% mRNAs were significantly decreased at 35 days in shunt-operated rats. The decrease in the SERCA mRNA level preceded the development of cardiac dysfunction. The levels of SERCA and ryanodine receptor mRNAs were correlated positively with left ventricular fractional shortening (r = 0.73, P < 0.0001 and r = 0.61, P < 0.01 respectively). Attenuation of the decrease in left ventricular fractional shortening occurred on %%%treatment%%% with TCV-116. After the %%%treatment%%% with TCV-116, the levels of SERCA and %%%phospholamban%%% mRNAs were restored to the respective values in sham-operated rats. Ryanodine receptor mRNA levels remained unchanged after %%%treatment%%% with TCV-116. These results indicate that the down-regulation of SERCA and ryanodine receptor mRNA levels may be related to card iac dysfunction in the volume-overloaded %%%heart%%%. In addition, %%%treatment%%% with an angiotensin II receptor antagonist may restore the altered sarcoplasmic reticulum mRNA levels to control levels, and this may result in attenuation of the functional impairment in the volume-overloaded %%%heart%%%.

4/7/25 (Item 3 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07466733 Genuine Article#: 169GW Number of References: 55
Title: Angiotensin type 1 receptor antagonism with irbesartan inhibits ventricular hypertrophy and improves diastolic function in the remodeling post-myocardial infarction ventricle
Author(s): Ambrose J; Pribnow DG; Giraud FD; Perkins KD; Muldoon L; Greenberg BH (REPRINT)
Corporate Source: UNIV CALIF SAN DIEGO,MED CTR, DIV CARDIOVASC MED, 200 W ARBOR DR/SAN DIEGO//CA/92103 (REPRINT); UNIV CALIF SAN DIEGO,MED CTR, DIV CARDIOVASC MED/SAN DIEGO//CA/92103; OREGON HLTH SCI UNIV,DIV CELL & DEV BIOL/PORTLAND//OR/97201; OREGON HLTH SCI UNIV,DIV CARDIOL/PORTLAND//OR/97201
Journal: JOURNAL OF CARDIOVASCULAR PHARMACOLOGY, %%%1999%%%, V33, N3 (MAR)
, P433-439
ISSN: 0160-2446 Publication date: 19990300
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106
Language: English Document Type: ARTICLE
Abstract: To evaluate the role of angiotensin II (AII) on diastolic function during post-myocardial infarction (MI) ventricular remodeling, coronary ligation or sham operation was performed in male Sprague-Dawley rats. Experimental animals were maintained on either irbesartan, a selective AT(1)-receptor antagonist, or no %%%treatment%%%. Measurement of cardiac hypertrophy, diastolic function, and sarcoendoplasmic reticulum adenosine triphosphatase (ATPase; SERCA) and %%%phospholamban%%% (PLB) gene expression was assessed at 6 weeks after MI. Myocardial infarction caused a significant increase in myocardial mass and left ventricular (LV) filling pressure, whereas LV systolic pressure and +dP/dt were reduced. The time constant of isovolumic relaxation (tau) was markedly prolonged after MI. Post-MI hypertrophy was associated with substantial increases in the messenger RNA (mRNA) expression of atrial natriuretic peptide (ANP), but no significant changes in SERCA or PLB levels. Although irbesartan %%%treatment%%% did not significantly alter post-MI LV systolic or filling pressures, it nevertheless effectively decreased ventricular hypertrophy, improved tau, and normalized ANP expression. These results demonstrate that AT(1)-receptor antagonism has important effects on myocardial hypertrophy and ANP gene expression, which are independent of ventricular loading conditions. In addition, the improvement in diastolic function was not related to changes in SERCA and PLB gene expression, suggesting that enhanced myocardial relaxation was related to the blockade of AII effects on myocyte function or through a reduction of ventricular hypertrophy itself or both.

4/7/26 (Item 4 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07380756 Genuine Article#: 158GX Number of References: 37
Title: Effect of angiotensin-converting enzyme inhibition on protein kinase C and SR proteins in %%%heart%%% %%%failure%%%
Author(s): Takeishi Y; Bhagwat A; Ball NA; Kirkpatrick DL; Periasamy M; Walsh RA (REPRINT)
Corporate Source: UNIV CINCINNATI,COLL MED, DIV CARDIOL, 231 BETHESDA AVE, RM 3354/CINCINNATI//OH/45267 (REPRINT); UNIV CINCINNATI,COLL MED, DIV CARDIOL/CINCINNATI//OH/45267
Journal: AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY, %%%1999%%%, V45, N1 (JAN), PH53-H62
ISSN: 0363-6135 Publication date: 19990100
Publisher: AMER PHYSIOLOGICAL SOC, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814
Language: English Document Type: ARTICLE
Abstract: We tested the hypothesis that activation of protein kinase C (PKC) isoforms in pressure-overload %%%heart%%% %%%failure%%% was prevented by angiotensin-converting enzyme (ACE) inhibition, resulting in normalization of cardiac sarcoplasmic reticulum (SR) Ca2+ ATPase (SERCA) 2a and %%%phospholamban%%% protein levels and improvement in intracellular Ca2+ handling. Aortic-banded and control guinea pigs were given ramipril (5 mg . kg(-1). day(-1)) or placebo for 8 wk. Ramipril-%%%treated%%% banded animals had lower left ventricular (LV) and lung weight, improved survival, increased isovolumic LV mechanics, and improved cardiomyocyte Ca2+ transients compared with placebo-%%%treated%%% banded animals. This was associated with maintenance of SERCA2a and %%%phospholamban%%% protein expression. Translocation of PKC-alpha and -epsilon was increased in placebo-%%%treated%%% banded guinea pigs compared with controls and was attenuated significantly by %%%treatment%%% with ramipril. We conclude that ACE inhibition attenuates PKC translocation and prevents downregulation of Ca2+ cycling protein expression in pressure-overload hypertrophy. This represents a mechanism for the beneficial effects of this therapy on LV function and survival in %%%heart%%% %%%failure%%%.

4/7/27 (Item 5 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07233888 Genuine Article#: 138KG Number of References: 25
Title: Effects of cyclic adenosine monophosphate (cAMP) on sarcoplasmic reticulum Ca2+-loading in failing rabbit and human cardiac trabeculae
Author(s): Denvir MA (REPRINT) ; MacFarlane NG; Miller DJ; Cobbe SM
Corporate Source: WESTERN GEN HOSP,DEPT CARDIOL/EDINBURGH EH4 2XU/MIDLOTHIAN/SCOTLAND/ (REPRINT); UNIV GLASGOW,INST BIOL & LIFE SCI/GLASGOW G12 8QQ/LANARK/SCOTLAND/; GLASGOW ROYAL INFIRM,DEPT MED CARDIOL/GLASGOW G4 0SF/LANARK/SCOTLAND/
Journal: BASIC RESEARCH IN CARDIOLOGY, %%%1998%%%, V93, N5 (OCT), P396-404
ISSN: 0300-8428 Publication date: 19981000
Publisher: DR DIETRICH STEINKOPFF VERLAG, PLATZ DER DEUTSCHEN EINHEIT 25, D-64293 DARMSTADT, GERMANY
Language: English Document Type: ARTICLE
Abstract: The response of cardiac SR Ca2+-loading to cAMP in failing rabbit and human myocardium was examined. Right ventricular (RV) trabeculae were isolated and mounted for isometric tension measurement. They were %%%treated%%% with saponin to permeabilise the sarcolemma but retain

SR
function, and bathed in a mock intracellular solution including adenosine triphosphate (ATP) and buffered calcium. Caffeine (10 mM) was used to release calcium from the SR. The amplitude of the caffeine-induced contracture was used as a quantitative gauge of the calcium content of the SR. Trabeculae were isolated from rabbits with coronary ligation-induced %%%heart%%% %%%failure%%% (LIG, n = 11), sham
operated controls (SW, n = 10), isoprenaline-infused rabbits (ISO, 7 days mini-osmotic pump 100 mu g/kg.h; n = 7) and saline-infused controls (SAL, n = 7). Failing human RV trabeculae were obtained at the time of cardiac transplantation. Failing rabbit trabeculae demonstrated increased baseline caffeine-induced contractures compared with controls, the response to cAMP was similar in the two groups (LIG 9.3 +/- 2.8 vs SH 10.6 +/- 3.2 % F-max; P = 0.55), There was no difference in the baseline SR Ca2+-loading in ISO trabeculae compared with SAL controls but there was a marked difference in the response to cAMP (11.1 +/- 5.4 vs 4.2 +/- 2.1 % F-max, P = 0.02). SR Ca2+-loading in failing human RV trabeculae was related to the severity of LV dysfunction (r = 0.59, P = 0.04) and demonstrated a marked cAMP-induced enhancement of caffeine-contracture (20.2 +/- 4.7 % increase of F-max) which was greater in patients with low compared with high ejection fraction. While beta-receptors are known to be down regulated in %%%heart%%% %%%failure%%% these results suggest that the scope for
cAMP-mediated enhancement of SR Ca2+-loading is maintained.

4/7/28 (Item 6 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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07220703 Genuine Article#: 138KH Number of References: 21
Title: Post-rest contraction amplitude in myocytes from failing human ventricle
Author(s): Davia K; Harding SE (REPRINT)
Corporate Source: UNIV LONDON IMPERIAL COLL SCI TECHNOL & MED,ROYAL
BROMPTON CAMPUS, DOVEHOUSE ST/LONDON SW3 6LY//ENGLAND/ (REPRINT); UNIV
LONDON IMPERIAL COLL SCI TECHNOL & MED,/LONDON SW3 6LY//ENGLAND/
Journal: BASIC RESEARCH IN CARDIOLOGY, %%%1998%%%, V93, 1, P33-37
ISSN: 0300-8428 Publication date: 19980000
Publisher: DR DIETRICH STEINKOPFF VERLAG, PLATZ DER DEUTSCHEN EINHEIT 25,
D-64293 DARMSTADT, GERMANY
Language: English Document Type: ARTICLE
Abstract: It has been reported that the balance between the two main Ca2+ removal systems in the cardiac cells, the sarcoplasmic reticulum (SR) and Na+/Ca2+ exchanger, is altered in failing human %%%heart%%%. We have studied postrest contraction behaviour as a noninvasive probe of the amount of Ca2+ stored in the SR in myocytes from failing and non-failing human ventricle. The first beat following a rest interval, as a percentage of the preceding steady state (B1/SS), was larger and more variable in cells from failing %%%heart%%%, indicating some accumulation of Ca2+ in the SR during rest. This could be mimicked by %%%treatment%%% of myocytes with digoxigenin, a compound which increases intracellular Na+, suggesting that alterations in the Na+ balance of the cell might contribute to the effect. Isoprenaline, which stimulates Ca2+ uptake by the SR while the myocyte is beating, prevented SR Ca2+ accumulation during rest in susceptible myocytes. We hypothesize that loss of SR function in the failing %%%heart%%% is partially compensated for by increased Ca2+ extrusion via the Na+/Ca2+ exchange in the contracting myocyte, leading to increased intracellular Na+ during activity. This Na+ is lost at rest, predisposing the cells to accumulate Ca2+ in the SR. Experiments to test this hypothesis are proposed.

4/7/29 (Item 7 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06642951 Genuine Article#: ZG794 Number of References: 38
Title: The role of CAMP in the frequency-dependent changes in contraction of guinea-pig cardiomyocytes
Author(s): MoneyKyrle ARW; Davies CH; Ranu HK; OGara P; Kent NS; PooleWilson PA; Harding SE (REPRINT)
Corporate Source: NATL HEART & LUNG INST,IMPERIAL COLL SCH MED, DOVEHOUSE
ST/LONDON SW3 6LY//ENGLAND/ (REPRINT); NATL HEART & LUNG INST,IMPERIAL
COLL SCH MED/LONDON SW3 6LY//ENGLAND/; JOHN RADCLIFFE HOSP,DEPT CARDIAC
MED/OXFORD OX3 9DU//ENGLAND/
Journal: CARDIOVASCULAR RESEARCH, %%%1998%%%, V37, N2 (FEB), P532-540
ISSN: 0008-6363 Publication date: 19980200
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE
Abstract: Objectives: beta-Receptor desensitisation, low basal cAMP, and a negative force-frequency relationship are characteristic changes in human %%%heart%%% %%%failure%%%. Isolated cardiomyocytes from noradrenaline-%%%treated%%% guinea pigs also show these features. We tested the hypothesis that low basal cAMP underlies the loss of contractile response to increasing stimulation frequency in this model, Methods: Isolated cardiomyocytes were obtained from noradrenaline-%%%treated%%% (NA) and sham-operated (SHAM) guinea. Figs. They were
stimulated from 0.1-2 Hz and contraction amplitude was monitored with a video edge-detection system. Results: NA cells had less positive amplitude-frequency responses (AFR) compared to SHAMs at 2 mM (P = 0.007, n = 17), or midrange Ca2+ concentrations (EC40-EC60)(P < 0.001, n = 13). When the cAMP agonist, 8-CPT-cAMP (CPT, 10 mu M) or high Ca2+ (above EC75) was added to NA cells the AFR was normalised to that of SHAM myocytes (NA vs. SHAM P = ns). In control experiments the CAMP antagonists, Rp-cAMPS (Rpc) and Rp-8-CPT-cAMPS (Rp8, 100 mu M), blocked
the positive inotropic effects of CPT at 0.5 Hz (control pD(2) = 4.36 +/- 0.06, Rp8 pD(2) = 3.68 +/- 0.08, P < 0.0001, n = 6 paired). Rpc (100 mu M) completely but reversibly blocked the effect of maximal isoprenaline in control experiments (P < 0.0001). Neither antagonist reduced the AFR compared to time-matched controls (P = ns, n = 6). Blockade of SERCA2a with thapsigargin resulted in a significant reduction in the AFR (ANOVA P < 0.0001). Conclusions: The results are consistent with sarcoplasmic reticulum (SR) function being a more important determinant of the amplitude-frequency relationship than tonic levels of CAMP under basal conditions. Reversal of AFR depression by CPT may result from stimulation of SRCa2+ uptake. (C) 1998 Elsevier Science B.V.

4/7/30 (Item 8 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06506210 Genuine Article#: YX731 Number of References: 36
Title: Effects of norepinephrine on expression of IGF-1/IGF-1R and SERCA2 in rat %%%heart%%%
Author(s): Sun XW; Ng YC (REPRINT)
Corporate Source: PENN STATE UNIV,MILTON S HERSHEY MED CTR, COLL MED, DEPT
PHARMACOL/HERSHEY//PA/17033 (REPRINT); PENN STATE UNIV,MILTON S HERSHEY
MED CTR, COLL MED, DEPT PHARMACOL/HERSHEY//PA/17033
Journal: CARDIOVASCULAR RESEARCH, %%%1998%%%, V37, N1 (JAN), P202-209
ISSN: 0008-6363 Publication date: 19980100
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE
Abstract: Objectives: The effects of norepinephrine on expression of cardiac genes during pathological cardiac growth and %%%heart%%% %%%failure%%% are not fully understood. Tissue insulin-like growth factor 1 (IGF-1) and its receptor (IGF-1R) play an important role in the regulation of the hyperplastic capacity of cardiac myocytes. Sarcoplasmic reticulum Ca2+-ATPase (SERCA2), on the other hand, is important in regulating cardiac contractile function. The present study examined the effects of elevated levels of NE on expression of

IGF-1/IGF-1R and SERCA2 mRNAs. Methods: Rats were infused with NE using
osmotic minipumps for 3 and 6 days at a rate of 50 mu g/kg/h and also at a higher dose (130 mu g/kg/h) for 6 and 14 days. Levels of expression of IGF-1/IGF-1R and SERCA2 mRNAs were determined by ribonuclease protection assay and by Northern blotting, respectively. Results: NE %%%treatment%%% significantly increased IGF-1 mRNA levels
in both left-and right-ventricle; however, levels of IGF-1R increased in the left-but not the right-ventricle. By contrast, NE infusion at both the lower dose and the higher dose failed to alter expression of SERCA2 mRNA. Conclusion: Our results suggest that NE %%%treatment%%%
differentially regulates expression of IGF-1 and IGF-1R in the ventricles of rat %%%heart%%% and that NE appears not to affect expression of SERCA2 mRNA. (C) 1998 Elsevier Science B.V.

4/7/31 (Item 9 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06506201 Genuine Article#: YX731 Number of References: 35
Title: Clenbuterol induces cardiac hypertrophy with normal functional, morphological and molecular features
Author(s): Wong K; Boheler KR; Bishop J; Petrou M; Yacoub MH (REPRINT)
Corporate Source: ROYAL BROMPTON HOSP,DEPT CARDIAC SURG, SYDNEY ST/LONDON
SW3 6NP//ENGLAND/ (REPRINT); UNIV LONDON IMPERIAL COLL SCI TECHNOL &
MED,NATL HEART & LUNG INST, DIV CARDIOTHORAC SURG/LONDON//ENGLAND/;
UNIV COLL LONDON,RAYNE INST, CTR CARDIOPULM BIOCHEM/LONDON//ENGLAND/
Journal: CARDIOVASCULAR RESEARCH, %%%1998%%%, V37, N1 (JAN), P115-122
ISSN: 0008-6363 Publication date: 19980100
Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS
Language: English Document Type: ARTICLE
Abstract: Objective: Several pharmacological agents have been shown to produce 'physiological' or 'pathological' hypertrophy based on their functional characteristics. The aim of this study was to examine the features of cardiac hypertrophy induced by the selective beta(2),-adrenergic agonist, clenbuterol. Methods: Cardiac hypertrophy was induced in 7 week-old Sprague-Dawley rats by daily injections of clenbuterol for 3 weeks. Thyroxine and isoproterenol were also used to produce cardiac hypertrophy to serve as positive controls for physiological and pathological hypertrophy, respectively. Left ventricular function was determined using an isolated rat %%%heart%%% preparation. Ventricular samples were used for morphological examination while interstitial collagen was measured using high-pressure liquid chromatography. Expression of sarcoplasmic reticulum Ca2+-ATPase2a (SERCA2a) and %%%phospholamban%%% (PLB) were
measured by dot blot analysis. Results: Clenbuterol %%%treatment%%% induced 26% left ventricular hypertrophy. These hearts demonstrated normal systolic isovolumic parameters and diastolic (active relaxation and passive stiffness) function, In addition, left ventricular concentration of collagen and morphology was normal as were the expression of SERCA2a and PLB mRNA. Conclusion: These results suggest that clenbuterol-induced hypertrophy is 'physiological' in terms of its function, extracellular structure and gene expression. (C) 1998 Elsevier Science B.V.

4/7/32 (Item 10 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06202458 Genuine Article#: YB623 Number of References: 44
Title: Phosphorylation of inhibitory subunit of troponin and
%%%phospholamban%%% in rat cardiomyocytes: Modulation by exposure of
cardiomyocytes to hydroxyl radicals and sulfhydryl group reagents
Author(s): Sulakhe PV (REPRINT) ; Vo XT; Phan TD; Morris TE
Corporate Source: UNIV SASKATCHEWAN,COLL MED, DEPT PHYSIOL, HLTH SCI BLDG,
107 WIGGINS RD/SASKATOON/SK S7N 5E5/CANADA/ (REPRINT)
Journal: MOLECULAR AND CELLULAR BIOCHEMISTRY, %%%1997%%%, V175, N1-2 (OCT)
, P99-107
ISSN: 0300-8177 Publication date: 19971000
Publisher: KLUWER ACADEMIC PUBL, SPUIBOULEVARD 50, PO BOX 17, 3300 AA
DORDRECHT, NETHERLANDS
Language: English Document Type: ARTICLE
Abstract: Myocytes were isolated from rat %%%heart%%% ventricles and then
incubated with [P-32]-sodium phosphate to label intracellular ATP stores, Incubations of the [P-32]-labelled cardiomyocytes with a beta-adrenoceptor agonist isoproterenol (10 mu M) and with a plant diterpene forskolin (100 mu M) Which directly stimulates adenylyl cyclase increased the phosphorylation of an inhibitory subunit of troponin (TN-I) and %%%phospholamban%%% (PLN), Brief exposure (1 min)
of labelled myocytes to the hydroxyl radical generating system (H2O2 plus FeCl2) decreased markedly the stimulatory action of isoproterenol and forskolin on TN-I and PLN phosphorylation. Similar exposure of myocytes to 5-5'-dithiobis-nitrobenzoic acid (DTNB) a sulfhydryl oxidizing reagent exerted little inhibitory effect on the isoproterenol or forskolin stimulated TN-I and PLN phosphorylation. In contrast exposure of myocytes to low concentrations (< 50 mu M) of N-ethylmaleimide (NEM) a sulfhydryl alkylating reagent augmented the stimulatory effect of isoproterenol on TN-I and PLN phosphorylation. The results further showed that brief %%%treatment%%% of myocytes to
H2O2 plus FeCl2 markedly decreased isoproterenol-, but not forskolin-, stimulated cyclic AMP accumulation in the myocytes. The stimulatory action of NEM on the isoproterenol-stimulated TN-I and PLN phosphorylation appeared related to greater increase in the isoproterenol-stimulated cyclic AMP accumulation in the NEM-%%%treated%%% cardiomyocytes. The results are consistent with the postulate that hydroxyl radical exposure of cardiomyocytes blunts the beta-adrenoceptor-mediated stimulation of adenylyl cyclase leading to decreased phosphorylation of TN-I and PLN and imply that such alterations account in part the reported depressed rate of relaxation of the myocardium exposed to oxygen free radicals.

4/7/33 (Item 11 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06188638 Genuine Article#: YA098 Number of References: 55
Title: Modulation of the renin-angiotensin pathway through enzyme inhibition and specific receptor blockade in pacing-induced %%%heart%%%
%%%failure%%% .2. Effects on myocyte contractile processes
Author(s): Spinale FG (REPRINT) ; Mukherjee R; Iannini JP; Whitebread S; Hebbar L; Clair MJ; Melton DM; Cox MH; Thomas PB; deGasparo M
Corporate Source: MED UNIV S CAROLINA,DIV CARDIOTHORAC SURG/CHARLESTON//SC/29425 (REPRINT); NOVARTIS,DIV PHARMACEUT/BASEL//SWITZERLAND/
Journal: CIRCULATION, %%%1997%%%, V96, N7 (OCT 7), P2397-2406
ISSN: 0009-7322 Publication date: 19971007
Publisher: AMER HEART ASSOC, 7272 GREENVILLE AVENUE, DALLAS, TX 75231-4596
Language: English Document Type: ARTICLE
Abstract: Background The goal of this study was to determine the effects of
ACE inhibition alone, AT(1) angiotensin (Ang) II receptor blockade alone, and combined ACEI and AT(1) Ang II receptor blockade in a model of congestive %%%heart%%% %%%failure%%% (CHF) on isolated LV myocyte
function and fundamental components of the excitation-contraction coupling process.

Methods and Results Pigs were randomly assigned to one of five groups: (1) rapid atrial pacing (240 bpm) for 3 weeks (n = 9), (2) concomitant ACEI (benazeprilat, 0.187 mg.kg(-1).d(-1)) and rapid pacing (n = 9), (3) concomitant AT(1) Ang II receptor blockade (valsartan, 3

mg/kg/d) and rapid pacing (n = 9), (4) concomitant ACEI and AT(1) Ang II receptor blockade (benazeprilat/valsartan, 0.05/3 mg.kg(-1).d(-1)) and rapid pacing (n = 9), and (5) sham controls (n = 10). LV myocyte shortening velocity was reduced with chronic rapid pacing compared with control (27.2 +/- 0.6 versus 58.6 +/- 1.2 mu/s, P < .05) and remained reduced with AT(1) Ang II receptor blockade and rapid pacing (28.0 +/- 0.5 mu m/s, P < .05). Myocyte shortening velocity increased with ACEI or combination %%%treatment%%% compared with rapid pacing only (36.9 +/- 0.7 and 42.3 +/- 0.8 mu m/s, respectively, P < .05). Myocyte beta-adrenergic response was reduced by > 50% in both the rapid pacing group and the AT(1) Ang II blockade group and improved by 25% with ACEI and increased by 54% with combined %%%treatment%%%. Both L-type Ca2+ channel density and the relative abundance of sarcoplasmic reticulum Ca2+ ATPase density were reduced with rapid pacing and returned to control levels in the combined ACEI and AT(1) Ang II blockade group.

Conclusions The unique findings of this study were twofold. First, basic defects in specific components of the myocyte excitation-contraction coupling process that occur with CHF are reversible. Second, combined ACEI and AT(1) Ang II blockade may provide unique benefits on myocyte contractile processes in the setting of CHF.

4/7/34 (Item 12 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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06162969 Genuine Article#: XZ012 Number of References: 70
Title: Interleukin-1 beta inhibits %%%phospholamban%%% gene expression in cultured cardiomyocytes
Author(s): McTiernan CF (REPRINT) ; Lemster BH; Frye C; Brooks S; Combes A; Feldman AM
Corporate Source: UNIV PITTSBURGH,DIV CARDIOL, MED CTR, BIOMED SCI TOWER 1744-1, 200 LOTHROP ST/PITTSBURGH//PA/15213 (REPRINT)
Journal: CIRCULATION RESEARCH, %%%1997%%%, V81, N4 (OCT), P493-503
ISSN: 0009-7330 Publication date: 19971000
Publisher: AMER HEART ASSOC, 7272 GREENVILLE AVENUE, DALLAS, TX 75231-4596
Language: English Document Type: ARTICLE
Abstract: %%%Phospholamban%%% is a key regulatory protein that defines diastolic function. Proinflammatory cytokines interleukin-1 beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-alpha) can depress contractility and intracellular Ca2+ currents and transients. An alteration in %%%phospholamban%%% expression is a possible pathway by which these cytokines modulate cardiac function. To test this hypothesis, primary cultures of neonatal rat cardiomyocytes were incubated with IL-1 beta, TNF-alpha, or both, and the level of %%%phospholamban%%% transcripts was examined by Northern blot analyses. %%%Phospholamban%%% transcript levels were decreased approximate to 50% (P<.0001) in cells exposed to 2 ng/mL IL-1 beta (20 hours), whereas TNF-alpha had no effect. Western blot analyses showed that IL-1 beta also reduced %%%phospholamban%%% protein levels (60% of control, P<.0001). The effects on transcript levels were gene specific; IL-1 beta induced transcripts for inducible NO synthase (iNOS), did not alter GAPDH transcripts, and reduced sarcoplasmic reticulum Ca?(2+)-ATPase (65% of control, P<.001) transcripts. Cardiomyocytes %%%treated%%% with IL-1 beta showed no alterations in basal contractile parameters (maximum velocity of contraction and relaxation and maximal amplitude of contraction) but were unresponsive to beta-adrenergic stimulation. Studies performed in the presence of second-messenger inhibitors showed that the effect of IL-1 beta on %%%phospholamban%%% transcript levels was blocked by dexamethasone, was insensitive to inhibitors of iNOS, cyclooxygenase, or tyrosine kinases, but was enhanced by the addition of the protein kinase inhibitor staurosporine. These data demonstrate that IL-1 beta alters the expression of %%%phospholamban%%%, a key regulator of cardiac contractility, at both the transcript and protein levels. The results suggest novel mechanisms by which IL-1 beta may modify cardiac function.

4/7/35 (Item 13 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05632049 Genuine Article#: WM203 Number of References: 40
Title: The effects of a thyroid hormone analog on left ventricular performance and contractile and calcium cycling proteins in the baboon
Author(s): Hoit BD; PawloskiDahm CM; Shao YF; Gabel M; Walsh RA (REPRINT)
Corporate Source: UNIV CINCINNATI,MED CTR, DIV CARDIOL, POB 670542/CINCINNATI//OH/45267 (REPRINT); UNIV CINCINNATI,MED CTR, DIV CARDIOL/CINCINNATI//OH/45267
Journal: PROCEEDINGS OF THE ASSOCIATION OF AMERICAN PHYSICIANS, %%%1997%%%, V109, N2 (MAR), P136-145
ISSN: 1081-650X Publication date: 19970300
Publisher: BLACKWELL SCIENCE INC, 350 MAIN ST, MALDEN, MA 02148
Language: English Document Type: ARTICLE
Abstract: To determine the biochemical and related functional effects of the thyroid hormone analog diiodothyropropionic acid (DITPA) on primate myocardium, we examined, both before and after 23 days of DITPA (3.75 mg/kg):myosin heavy-chain (MHC) isoforms and sarcoplasmic reticulum (SR) calcium cycling proteins; left ventricular (LV) function; and the LV force-frequency relation in four baboons chronically instrumented with sonomicrometers and micromanometers. The force-frequency relation was measured as the response of isovolumic contraction (dP/dt(max)) to incremental pacing and the critical %%%heart%%% rate (HR(crit)) as the rate at which dP/dt(max) reached its maximum. DITPA increased basal LV dP/dt(max) (3300 +/- 378 versus 2943 +/- 413 mm Hg/sec; p = .09), and velocity of circumferential shortening (1.13 +/- 0.30 versus 0.76 +/- 0.30 circ/sec; p < .01), decreased the basal time constant of isovolumic relaxation (24.2 +/- 1.6 versus 29.9 +/- 2.5 msec; p < .05), and increased the HR(crit) (203 +/- 19 versus 168 +/- 20 bpm; p < .05), without effecting significant changes in either basal %%%heart%%% rate (119 +/- 14 versus 111 +/- 17 bpm) or systolic blood pressure (137 +/- 14 versus 126 +/- 8 mm Hg). Quantitative immunoblotting revealed significant decreases in both %%%phospholamban%%% and the ratio of %%%phospholamban%%% to SR Ca2+ adenosine triphosphatase in DITPA-%%%treated%%% animals when compared to four untreated controls. By contrast, alpha-MHC isoform was undetectable in both DITPA %%%treated%%% and control baboons. Thus, DITPA favorably alters the stoichiometry between the SR calcium pump and its inhibitor, %%%phospholamban%%%, and has positive inotropic and lusitropic effects in the normal primate left ventricle, which may be useful in the %%%treatment%%% of %%%heart%%% %%%failure%%%. Unlike thyroid hormone, these changes occur in the absence of detectable alpha-MHC isoform protein expression and without an increase in %%%heart%%% rate.

4/7/36 (Item 14 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05252356 Genuine Article#: VL228 Number of References: 51
Title: EFFECTS OF THYROID-HORMONE ON LEFT-VENTRICULAR PERFORMANCE AND REGULATION OF CONTRACTILE AND CA2(+)-CYCLING PROTEINS IN THE BABOON - IMPLICATIONS FOR THE FORCE-FREQUENCY AND RELAXATION-FREQUENCY

RELATIONSHIPS
Author(s): KHOURY SF; HOIT BD; DAVE V; PAWLOSKIDAHM CM; SHAO Y; GABEL M;
PERIASAMY M; WALSH RA
Corporate Source: UNIV CINCINNATI,MED CTR,DIV CARDIOL,POB 670542/CINCINNATI//OH/45267; UNIV CINCINNATI,MED CTR,DIV CARDIOL/CINCINNATI//OH/45267
Journal: CIRCULATION RESEARCH, %%%1996%%%, V79, N4 (OCT), P727-735
ISSN: 0009-7330
Language: ENGLISH Document Type: ARTICLE
Abstract: The transcriptional, posttranscriptional, and related functional effects of thyroid hormone on primate myocardium are poorly understood. Therefore, we studied the effects of thyroid hormone on sarcoplasmic reticulum (SR) Ca2+-cycling proteins and myosin heavy chain (MHC) composition at the steady state mRNA and protein level and associated alterations of left ventricular (LV) performance in 8 chronically instrumented baboons. The force-frequency and relaxation-frequency relations were assessed as the response of LV isovolumic contraction (dP/dt(max)) and relaxation (Tau), respectively, to incremental atrial pacing. Both the %%%heart%%% rate at which dP/dt(max) was maximal and
Tau was minimal (critical %%%heart%%% rates) in response to pacing were
increased significantly after thyroid hormone. Postmortem LV tissue from 5 thyroid-%%%treated%%% and 4 additional control baboons was assayed for steady state mRNA levels with cDNA probes to MHC isoforms
and SR Ca2+-cycling proteins. Steady state SR Ca2+-ATPase and %%%phospholamban%%% mRNA increased in the hyperthyroid state, and alpha-MHC mRNA appeared de novo, whereas beta-MHC mRNA decreased.
Western analysis (4 thyroid-%%%treated%%% and 4 control baboons) showed
directionally similar changes in MHC isoforms and a slight increase in SR Ca2+-ATPase. In contrast, there was a statistically nonsignificant decrease in %%%phospholamban%%% protein, which resulted in a significant 40% decrease in the ratio of %%%phospholamban%%% to SR Ca2+-ATPase. Thus, thyroid hormone increases the transcription of Ca2+-cycling proteins and shifts MHC isoform expression in the primate LV. Our data suggest that both transcriptional and posttranslational mechanisms determine the levels of these proteins in the hyperthyroid primate %%%heart%%% and mediate, in part, the observed enhanced basal
and frequency-dependent LV performance.

4/7/37 (Item 15 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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05231238 Genuine Article#: VJ617 Number of References: 21
Title: EFFECTS OF CANTHARIDIN ON FORCE OF CONTRACTION AND PHOSPHATASE-ACTIVITY IN NONFAILING AND FAILING HUMAN HEARTS
Author(s): LINCK B; BOKNIK P; KNAPP J; MULLER FU; NEUMANN J; SCHMITZ W;
VAHLENSIECK U
Corporate Source: UNIV MUNSTER,INST PHARMAKOL & TOXIKOL,DOMAGKSTR12/D-48149 MUNSTER//GERMANY/; UNIV MUNSTER,INST PHARMAKOL & TOXIKOL/D-48149 MUNSTER//GERMANY/
Journal: BRITISH JOURNAL OF PHARMACOLOGY, %%%1996%%%, V119, N3 (OCT), P
545-550
ISSN: 0007-1188
Language: ENGLISH Document Type: ARTICLE
Abstract: 1 The effect of the phosphatase inhibitor, cantharidin (3-300 mu M) on force of contraction was studied in isolated electrically driven right ventricular trabeculae carneae from human myocardium.

2 The positive inotropic effect of cantharidin started at a concentration of 100 mu M with a positive inotropic effect to 199% and to 276% of the predrug value in nonfailing and failing human hearts, respectively.

3 Under basal conditions the contraction time parameters were prolonged in human %%%heart%%% %%%failure%%% vs. nonfailing preparations. However, the positive inotropic effect of cantharidin did not affect contraction time parameters. Thus, time to peak tension, time of relaxation and total contraction time were not shortened by cantharidin in nonfailing and failing preparations.

4 The phosphatase activity was unchanged in preparations from failing hearts compared to nonfailing hearts.

5 Cantharidin inhibited phosphatase activity in a concentration-dependent manner. The IC50 value of cantharidin was about
3 mu M in both nonfailing and failing human myocardium.

6 The positive inotropic effect of cantharidin was similar in nonfailing and failing human hearts, accompanied by a similar inhibitory effect of cantharidin on the phosphatase activity. The positive inotropic effect of cantharidin in failing hearts was as strong as the effect of isoprenaline in nonfailing hearts.

7 It is concluded that the %%%treatment%%% with a phosphatase inhibitor may offer a new positive inotropic modality for the %%%treatment%%% of human %%%heart%%% %%%failure%%%.

4/7/38 (Item 16 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03542982 Genuine Article#: PL355 Number of References: 117
Title: PHYSIOLOGICAL AND PHARMACOLOGICAL FACTORS THAT AFFECT MYOCARDIAL
RELAXATION
Author(s): VITTONE L; MUNDINAWEILENMANN C; MATTIAZZI A; CINGOLANI H
Corporate Source: NATL UNIV LA PLATA,FAC CIENCIAS MED,CTR INVEST CARDIOVASC,60 & 120/RA-1900 LA PLATA//ARGENTINA/; NATL UNIV LA PLATA,FAC CIENCIAS MED,CTR INVEST CARDIOVASC/RA-1900 LA PLATA//ARGENTINA/
Journal: JOURNAL OF PHARMACOLOGICAL AND TOXICOLOGICAL METHODS, %%%1994%%%
, V32, N1 (SEP), P7-18
ISSN: 1056-8719
Language: ENGLISH Document Type: REVIEW
Abstract: Evaluation of the myocardial relaxation has become important in the last years. Pm impaired relaxation may precede contractile dysfunctions and even cause %%%heart%%% %%%failure%%%. To %%%treat%%%
this impaired lusitropism it is necessary to properly assess the lusitropic state of the %%%heart%%% and understand how drugs affect the
cellular mechanisms underlying myocardial relaxation (sarcoplasmic reticulum function, Ca2+ fluxes through the sarcolemma and myofilament Ca2+ sensitivity). Current information regarding these issues is provided in this review. The relative usefulness of the mechanical parameters used to evaluate the lusitropic state of the %%%heart%%% in experimental models applied in pharmacology will also be discussed.

4/7/39 (Item 17 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03476580 Genuine Article#: PG537 Number of References: 47
Title: THYROID-HORMONE ENHANCES CA2+ PUMPING ACTIVITY OF THE CARDIAC
SARCOPLASMIC-RETICULUM BY INCREASING CA2+ ATPASE AND DECREASING
%%%PHOSPHOLAMBAN%%% EXPRESSION
Author(s): KIMURA Y; OTSU K; NISHIDA K; KUZUYA T; TADA M
Corporate Source: OSAKA UNIV,SCH MED,DEPT MED & PATHOPHYSIOL,2-2
YAMADAOKA/SUITA/OSAKA 565/JAPAN/; OSAKA UNIV,SCH

MED,DEPT MED &
PATHOPHYSIOL/SUITA/OSAKA 565/JAPAN/
Journal: JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY, %%%1994%%%, V26, N9
(SEP), P1145-1154
ISSN: 0022-2828
Language: ENGLISH Document Type: ARTICLE
Abstract: %%%Phospholamban%%% is a putative suppressor of the Ca2+ ATPase
of the cardiac sarcoplasmic reticulum. The level of mRNA encoding the Ca2+ ATPase has been shown to be increased, whereas the %%%phospholamban%%% mRNA level to be decreased in the ventricles obtained from hyperthyroid rabbits [Nagai R, Zarain-Herzberg A, Brandl CJ, Fujii J, Tada M, MacLennan DH, Alpert NR, Periasamy M. (1989) Proc Natl Acad Sci USA 86: 2966-2970]. The present study was designed to examine whether these effects of thyroid hormone on the expression of the Ca2+ ATPase and %%%phospholamban%%% are exerted directly on cardiac
myocytes and whether the resultant incoordinate expression of these proteins alters Ca2+ pumping activity. We studied the levels of %%%phospholamban%%% and Ca2+ ATPase mRNA in primary isolated neonatal
rat myocardial cells incubated with triiodothyronine (T-3) for 3-48 h and the Ca2+ uptake activity of the microsomes prepared from the cells. Northern blot analysis showed that T-3 decreased %%%phospholamban%%%
mRNA levels to about a half of control in 24 h. On the other hand, Ca2+ ATPase mRNA gradually increased with time. EC(50) for %%%phospholamban%%% mRNA expression was 2.5 x 10(-10) M which was
approximately 10 times higher than that for the Ca2+ ATPase. T-3 increased V-max of Ca2+ uptake with the significant reduction of K-0.5 for Ca2+ (0.40 +/- 0.02 mu M for control v 0.31 +/- 0.02 mu M for T-3-%%%treated%%% vesicles), indicating that thyroid hormone stimulates Ca2+ pumping activity not only by increasing the Ca2+ ATPase but also decreasing %%%phospholamban%%%. These results suggested that %%%phospholamban%%% regulates the Ca2+ ATPase in dual modes; in short
time range, by decreasing the affinity of the Ca2+ ATPase for Ca2+ by phosphorylation of %%%phospholamban%%% with cAMP-dependent protein
kinase, and in long time range, by changing the molecular ratio between the two proteins through the regulation of gene expression.

4/7/40 (Item 18 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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01748543 Genuine Article#: HY053 Number of References: 29
Title: REVERSIBLE ALTERATIONS IN MYOCARDIAL GENE-EXPRESSION IN A YOUNG MAN
WITH DILATED CARDIOMYOPATHY AND HYPOTHYROIDISM
Author(s): LADENSON PW; SHERMAN SI; BAUGHMAN KL; RAY PE; FELDMAN AM
Corporate Source: JOHNS HOPKINS UNIV,SCH MED,DEPT MED,DIV CARDIOL,RICHARD S
ROSS RES BLDG,ROOM 835,725 N WOLFE ST/BALTIMORE//MD/21205; JOHNS
HOPKINS UNIV,SCH MED,DEPT MED,DIV CARDIOL,RICHARD S ROSS RES BLDG,ROOM
835,725 N WOLFE ST/BALTIMORE//MD/21205; JOHNS HOPKINS UNIV,SCH MED,DEPT
MED,DIV ENDOCRINOL & METAB/BALTIMORE//MD/21205; JOHNS HOPKINS UNIV,SCH
MED,DEPT MED,PETER BELFER LAB MOLEC BIOL HEART FAILURE/BALTIMORE//MD/21205
Journal: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED
STATES OF AMERICA, %%%1992%%%, V89, N12 (JUN 15), P5251-5255
Language: ENGLISH Document Type: ARTICLE
Abstract: Thyroid hormone effects on myocardial gene expression have been well defined in animal models, but their relationship to the pathogenesis of cardiac dysfunction in hypothyroid humans has been uncertain. We evaluated a profoundly hypothyroid young man with dilated cardiomyopathy. Before and during 9 months of thyroxine therapy, serial assessment of myocardial performance documented substantial improvements in the left ventricular ejection fraction (16-37%), left ventricular end-diastolic diameter (7.8-5.9 cm), and cardiac index (1.4-2.7 liters-min-1.m-2). Steady-state levels of mRNAs encoding selected cardiac proteins were measured in biopsy samples obtained before and after thyroxine replacement. In comparison with myocardium from nonfailing control hearts, this patient's pretreatment alpha-myosin heavy-chain mRNA level was substantially lower, the atrial natriuretic factor mRNA level was markedly elevated, and the %%%phospholamban%%% mRNA level was decreased. All of these derangements
were reversed 9 months after restoration of euthyroidism. These observations in an unusual patient with profound myxedema and cardiac dilatation permit correlation between the reversible changes in myocardial function and steady-state mRNA levels in a cardiomyopathy. They suggest that alterations in gene expression in the dilated myopathic %%%heart%%% may be correctable when a %%%treatable%%% cause
is identified.

4/7/41 (Item 19 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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01042460 Genuine Article#: FQ593 Number of References: 22
Title: THE RELATIVE EFFICIENCY OF BETA-ADRENOCEPTOR COUPLING TO MYOCARDIAL
INOTROPY AND DIASTOLIC RELAXATION - ORGAN-SELECTIVE %%%TREATMENT%%% FOR
DIASTOLIC DYSFUNCTION
Author(s): KENAKIN TP; AMBROSE JR; IRVING PE
Corporate Source: GLAXO INC,GLAXO RES INST,DIV PHARMACOL,5 MOORE DR/RES
TRIANGLE PK//NC/27709
Journal: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, %%%1991%%%
, V257, N3, P1189-1197
Language: ENGLISH Document Type: ARTICLE
Abstract: The relative effects of drugs which elevate cytosolic cyclic AMP on inotropy and diastolic relaxation (lusitropy) of guinea pig atria were quantified in vitro. There was a temporal difference between these responses in that inotropy reached peak response considerably faster than lusitropy. Also, although the relaxation response was sustained to an elevated steady state, the inotropic responses to beta adrenoceptor agonists were transient and returned to base line over 90 min. However, the inotropic responses to forskolin and dibutyryl cyclic AMP (cAMP) were sustained. For all of the drugs tested, the lusitropic response was at least 4 times more sensitive than the inotropic response (i.e., the concentration response curve for relaxation was shifted to the left of the curve for inotropy). In the case of beta adrenoceptor agonists, these differences were greater, presumably because of the fading inotropic response over 90 min. It was found that although high efficacy beta adrenoceptor agonists such as isoproterenol (and the direct activator of adenylate cyclase forskolin) produced both inotropy and lusitropy, lower efficacy agonists produced predominant lusitropy. The low efficacy agonist prenalterol produced insignificant inotropy but 60% maximal lusitropy. These data were modeled mathematically by a "differential coupling model" which assumed that a uniform cytosolic level of elevated cAMP activated two biochemical processes of differing sensitivity. Thus, the lusitropic response (phosphorylation of %%%phospholamban%%%) was coupled more efficiently to the cAMP response than the inotropic response (phosphorylation of calcium channels). A second model ("differential messenger concentration model") which calculated the effects of a compartmentalization of cAMP concentration within the cardiac cell by restricted diffusion and/or selective degradation by phosphodies-terases also was used. The implications of these data are discussed in terms of the choice of tissue response used to measure agonist potency and/or efficacy and the possible use of differentially coupled physiological responses to achieve selective drug %%%treatment%%%.

4/7/42 (Item 1 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

01226178 1999202583
Captopril %%%treatment%%% improves the sarcoplasmic reticular Casup 2sup +
transport in %%%heart%%% %%%failure%%% due to myocardial infarction
Shao Q.; Ren B.; Zarain-Herzberg A.; Ganguly P.K.; Dhalla N.S.
ADDRESS: N.S. Dhalla, Institute of Cardiovascular Sciences, St. Boniface General Hosp. Res. Ctr., 351 Tache Avenue, Winnipeg, Man. R2H 2A6, Canada
Journal: Journal of Molecular and Cellular Cardiology, 31/9 (1663-1672), %%%1999%%%, United Kingdom
CODEN: JMCDA
ISSN: 0022-2828
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 40

Although captopril, an angiotensin-converting enzyme (ACE) inhibitor, has been shown to exert a beneficial effect on cardiac function in %%%heart%%%
%%%failure%%%, its effect on the status of sarcoplasmic reticulum (SR) Casup 2sup + transport in the failing %%%heart%%% has not been examined previously. In order to determine whether captopril has a protective action on cardiac function, as well as cardiac SR Casup 2sup +-pump activity and gene expression, a rat model of %%%heart%%% %%%failure%%% due to myocardial
infarction was employed in this study. Sham operated and infarcted rats were given captopril (2 g/l in drinking water; this %%%treatment%%% was started at either 3 or 21 days and was carried out until 8 weeks after the surgery. The untreated animals with myocardial infarction showed increased %%%heart%%% weight and elevated left ventricular end diastolic pressure, reduced rates of pressure development and pressure fall, as well as depressed SR Casup 2sup + uptake and Casup 2sup +-stimulated ATPase activities in comparison with the sham control group. These hemodynamic and
biochemical changes in the failing hearts were prevented by %%%treatment%%%
of the infarcted animals with captopril. Likewise, the observed reductions in the SR Casup 2sup + pump and %%%phospholamban%%% protein contents, as
well as in the mRNA levels for SR Casup 2sup + pump ATPase and %%%phospholamban%%%, in the failing %%%heart%%% were attenuated by captopril %%%treatment%%%. These results suggest that %%%heart%%% %%%failure%%% is associated with a defect in the SR Casup 2sup + handling and a depression in the gene expression of SR proteins: the beneficial effect of captopril in %%%heart%%% %%%failure%%% may be due to its ability
to prevent remodeling of the cardiac SR membrane.

4/7/43 (Item 2 from file: 71)
DIALOG(R)File 71:ELSEVIER BIOBASE

00719796 97224683
Thyroid hormone improves function and Casup 2sup + handling in pressure overload hypertrophy. Association with increased sarcoplasmic reticulum Casup 2sup +-ATPase and alpha-myosin heavy chain in rat hearts
Chang K.C.; Figueredo V.M.; Schreur J.H.M.; Kariya K.-I.; Weiner M.W.; Simpson P.C.; Camacho S.A.
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Hospital, San Francisco, CA 94110, United States
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Journal: Journal of Clinical Investigation, 100/7 (1742-1749), %%%1997%%%,
United States
PUBLICATION DATE: 19970000
CODEN: JCINA
ISSN: 0021-9738
DOCUMENT TYPE: Article
LANGUAGES: English SUMMARY LANGUAGES: English
NO. OF REFERENCES: 50

We asked whether thyroid hormone (Tinf 4) would improve %%%heart%%% function in left ventricular hypertrophy (LVH) induced by pressure overload (aortic banding). After banding for 10-22 wk, rats were %%%treated%%% with
Tinf 4 or saline for 10-14 d. Isovolumic LV pressure and cytosolic (Casup 2sup +) (indo-1) were assessed in perfused hearts. Sarcoplasmic reticulum Casup 2sup +-ATPase (SERCA), %%%phospholamban%%%, and alpha- and beta-myosin heavy chain (MHC) proteins were assayed in homogenates of myocytes isolated from the same hearts. Of 14 banded hearts %%%treated%%%
with saline, 8 had compensated LVH with normal function (LVH(comp)), whereas 6 had abnormal contraction, relaxation, and calcium handling (LVH(decomp)). In contrast, banded animals %%%treated%%% with Tinf 4 had no
myocardial dysfunction; these hearts had increased contractility, and faster relaxation and cytosolic (Casup 2sup +) decline compared with LVH(comp) and LVH(decomp). Myocytes from banded hearts %%%treated%%% with
Tinf 4 were hypertrophied but had increased concentrations of alpha-MHC and
SERCA proteins, similar to physiological hypertrophy induced by exercise. Thus thyroid hormone improves LV function and calcium handling in pressure overload hypertrophy, and these beneficial effects are related to changes in myocyte gene expression. Induction of physiological hypertrophy by thyroid hormone-like signaling might be a therapeutic strategy for %%%treating%%% cardiac dysfunction in pathological hypertrophy and %%%heart%%% %%%failure%%%.

4/7/44 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

10600004 EMBASE No: 2000065247
Receptor-mediated signal transduction and drug development: Angiotensin II-mediated signal transduction, ATinf 1 receptor antagonists and ACE inhibitors in congestive %%%heart%%% %%%failure%%%
Endoh M.; Sakurai K.; Tomoike H.
M. Endoh, Department of Pharmacology, Yamagata Univ. School of Medicine,
2-2-2 Iida-nishi, Yamagata 990-9585 Japan
Pharmacometrics (PHARMACOMETRICS) (Japan) 1999, 58/1 (1-15)
CODEN: OYYAA ISSN: 0300-8533
DOCUMENT TYPE: Journal; Article
LANGUAGE: JAPANESE SUMMARY LANGUAGE: ENGLISH; JAPANESE

Various types of receptor are distributed on the surface membrane of myocardial cells, which are activated by neurotransmitters, neuropeptides, autacoids and cytokines to lead to the subsequent functional and metabolic adaptation, and altered gene expression and synthesis of functional proteins of the %%%heart%%%. Among these regulatory mechanisms, angiotensin
II (Ang II) plays an extremely important role in induction of cardiac hypertrophy and congestive %%%heart%%% %%%failure%%% (CHF). Therapeutic
agents that modulate the Ang II- mediated signal transduction are effective
in the %%%treatment%%% of patients with CHF. Ang II receptors belong to a
family of seven transmembrane G protein coupled receptors. Ang II receptors
exist in cardiac tissue, on cell membranes of various types of cells, including myocardial cells, sympathetic nerve endings, fibroblasts, coronary artery smooth muscle and endothelial cells. Two subtypes of Ang II receptors (ATinf 1, ATinf 2) have been cloned. Cardiovascular regulation is mediated largely by activation of ATinf 1 receptors. Intracellular transduction processes triggered by activation of ATinf 1 receptors involve divergent pathways, such as acceleration of PI hydrolysis through activation of PLCbeta by Gq and PLCgamma by tyrosine phosphorylation, and activation of various enzymes, which lead to (1) immediate alteration of activity of ion channels and ion exchangers, and intracellular alkalinization; and (2) long-term regulation of gene expression and protein synthesis that is responsible for cardiac hypertrophy and vascular and cardiac remodeling. ATinf 2 receptors regulate also various processes in cardiovascular cells, including growth inhibition, proapoptosis, cell differentiation, decrease in cellular matrix in the %%%heart%%%, inhibition of cell proliferation, NO production and decrease in cardiac chronotropic

effect. The Ang II-mediated regulation of cardiac function and gene expression, and the characteristics of pharmacological agents that affect the Ang II-mediated signaling process are reviewed in relation to the state-of- the-art of pharmacological therapy of CHF and perspectives of development of novel therapeutic agents for CHF.

4/7/45 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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07884580 EMBASE No: 1999340513
Elevated levels of endogenous adenosine alter metabolism and enhance reduction in contractile function during low-flow ischemia: Associated changes in expression of Casup 2sup +-ATPase and %%%phospholamban%%%
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DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 68

Adenosine has several potentially cardioprotective effects including vasodilation, reduction in %%%heart%%% rate and alterations in metabolism. Adenosine inhibits catecholamine-induced increase in contractile function mainly through inhibition of phosphorylation of %%%phospholamban%%% (PLB),
the main regulators protein of Casup 2sup +-ATPase in sarcoplasmic reticulum (SR), and during ischemia it reduces calcium (Casup 2sup +) overload. In this study we examined the effects of endogenous adenosine on contractile function and metabolism during low-flow ischemia (LFI) and investigated whether endogenous adenosine can alter expression of the Casup
2sup +- ATPase/PLB-system and other Casup 2sup +-regulatory proteins. Isolated blood-perfused piglet hearts underwent 120 mm 10% flow. Hearts were %%%treated%%% with either saline, the adenosine receptor blocker (8)-sulfophenyl theophylline (8SPT, 300 mumol/l) or the nucleoside transport inhibitor draflazine (1 mumol/l). During LFI, 8SPT did not substantially influence metabolic or functional responses. However, draflazine enhanced the reduction in %%%heart%%% rate, contractile force and MVOinf 2, with less release of Hsup + and COinf 2. Before LFI there were no significant differences between groups for any of the proteins (Casup 2sup +-ATPase, ryanodine-receptor, Nasup +/Ksup +-ATPase) or mRNAs
(Casup 2sup +- ATPase, PLB, calsequestrin, Nasup +/Casup 2sup +-exchanger) measured. At end of LFI mRNA-level of PLB was higher in draflazine-%%%treated%%% hearts compared to both other groups (P < 0.01 vs both). Also, at end of LFI protein-level of Casup 2sup +-ATPase was lower in draflazine-%%%treated%%% hearts (P < 0.05 vs both), and a parallel trend towards a lower mRNA-level was seen (P = 0.11 vs saline and P = 0.43 vs 8SPT). During LFI tissue Casup 2sup + tended to rise in saline- and 8SPT-%%%treated%%% hearts but not in draflazine-%%%treated%%% hearts (at end of
LFI, P = 0.01 vs 8SPT). We conclude that the amount of adenosine normally produced during LFI does not substantially influence function and metabolism However, increased endogenous levels by draflazine enhance downregulation of function and reduce signs of anaerobic metabolism. At end of LFI associated changes in expression of PLB and Casup 2sup +-ATPase were
seen. The functional significance was not determined in the present study. However, altered protein-levels might influence Casup 2sup +-handling in sarcoplasmic reticulum and thus affect contractile force and tolerance to ischemia.

4/7/46 (Item 3 from file: 73)
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07844535 EMBASE No: 1999093709
Thyroid hormone control of contraction and the Casup 2sup +-ATPase/%%%phospholamban%%% complex in adult rat ventricular myocytes
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Journal of Molecular and Cellular Cardiology (J. MOL. CELL. CARDIOL.) (United Kingdom) 1999, 31/3 (645-656)
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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 30

Thyroid hormones may have important long-term effects on cellular Casup 2sup + handling in the %%%heart%%%. We investigated isolated adult rat cardiomyocytes in a primary culture exposed (Tinf 3-cells) or not exposed to (control cells) 10sup -sup 8 M triiodothyronine (Tinf 3) for 48 h. Northern blot analysis revealed reciprocal alterations in the expression of SERCA2 and %%%phospholamban%%%. The ratio of the SERCA2/%%%phospholamban%%%
signal was ~ 10 times higher in the Tinf 3-cells as compared with the control cells (P < 0.05). %%%Phospholamban%%% protein content was significantly reduced by 33% but SR-Casup 2sup +-ATPase protein content was
not significantly altered in Tinf 3-cells. These results were associated with functional alterations measured by an inverted microscope equipped to monitor fluorescence at two excitation wavelengths as well as cell shortening by a video edge detection unit. The peak calcium transients as measured by fura-2 acetoxymethyl ester (AM) were increased significantly during stimulation at 0.25 and 0.5 Hz in Tinf 3-cells compared with control cells (P < 0.05). The monoexponential decline of the fura-2 transient was significantly faster at all frequencies in the Tinf 3-cells as compared with control cells (P < 0.05). Interesting, we observed blunted responses to both isoproterenol stimulation and post rest potentiation in the Tinf 3-cells. The intracellular level of sodium as represented by SBFI-AM was significantly lower in the Tinf 3-cells compared with the control cells (P < 0.05). The increased SR-Casup 2sup +-ATPase/%%%phospholamban%%% ratio and
decrease in %%%phospholamban%%% protein content in Tinf 3-%%%treated%%%
cells was reflected in a parallel increase of contraction and calcium transients and more rapid Casup 2sup + reuptake, but the post-rest potentiation and response to isoproterenol were reduced.

4/7/47 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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07726984 EMBASE No: 1999203852
Minimal amount of insulin can reverse diabetic %%%heart%%% function: Sarcoplasmic reticulum Casup 2sup + transport and %%%phospholamban%%% protein expression
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CODEN: KJPPF ISSN: 1226-4512
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 33

In the present study, the underlying mechanisms for diabetic functional derangement and insulin effect on diabetic cardiomyopathy were investigated
with respect to sarcoplasmic reticulum (SR) Casup 2sup +-ATPase and %%%phospholamban%%% at the transcriptional and translational levels. The maximal Casup 2sup + uptake and the affinity of Casup 2sup +-ATPase for Casup 2sup + were decreased in streptozotocin-induced diabetic rat cardiac SR, however, even minimal amount of insulin could reverse both parameters. Levels of both mRNA and protein of %%%phospholamban%%% were significantly
increased in diabetic rat hearts, whereas the mRNA and protein levels of SR Casup 2sup +-ATPase were significantly decreased. In case of %%%phospholamban%%%, insulin %%%treatment%%% reverses these parameters to

normal levels. Minimal amount of insulin could reverse the protein levels; however, it could not reverse the mRNA level of SR Casup 2sup +-ATPase at all. Thus, the decreased SR Casup 2sup + uptake appear to be largely attributed to the decreased SR Casup 2sup +-ATPase level, which is further impaired due to the inhibition by the increased level of %%%phospholamban%%%. These results indicate that insulin is involved in the
control of intracellular Casup 2sup + in the cardiomyocyte through multiple target proteins via multiple mechanisms for the decrease in the mRNA for both SR Casup 2sup +-ATPase and %%%phospholamban%%% which are unknown and
needs further study.

4/7/48 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE
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07567161 EMBASE No: 1999032115
Genetically engineered mice: Model systems for left ventricular %%%failure%%%
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Journal of Cardiac Failure (J. CARD. FAIL.) (United States) 1998, 4/4 (349-361)
CODEN: JCFAF ISSN: 1071-9164
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 59

The advent of mouse genetic manipulation coupled with the development of miniaturized technology to characterize the obtained phenotypes have provided significant insights into the genetic mechanisms underlying cardiovascular function in health and %%%disease%%%. It is now obvious that
alterations of the expression (decreased or increased) levels or function of a single gene, as outlined in this review, may result in cardiac hypertrophy and/or %%%failure%%%. Thus, a number of '%%%heart%%% %%%failure%%% candidate genes' have been identified. However, characterization of their corresponding mouse phenotypes has indicated that
there is a compensatory 'cross-talk' between a specific 'candidate gene' and various other genes, resulting in altered expression of multiple gene products, which may mask or contribute to the observed %%%heart%%% %%%failure%%% phenotype. Further studies using new advances in transgenic
mouse technology, which allow for tissue-specific ablation or tissue-specific inducible expression of targeted gene products along with introduction of specific mutations in the gene of interest, hold promise for identifying a single or a cluster of 'candidate genes' for %%%heart%%% %%%failure%%%. Nevertheless, the rapid development and characterization of
the various mouse models described in this article have provided meaningful new information on the molecular mechanisms underlying cardiac function and
dysfunction. Furthermore, these models have lent valuable insights into genetic targets for %%%treatment%%% of %%%heart%%% %%%disease%%%. As noted
earlier, overexpression of the beta2-adrenergic receptor or its kinase inhibitor, overexpression of SR Casup 2sup +-ATPase, or downregulation of %%%phospholamban%%% expression may each result in improved contractility
and this may be beneficial for the %%%treatment%%% of the failing %%%heart%%%. In addition, the involvement of the calcineurin pathway in the
cause/progression of %%%heart%%% %%%disease%%% will undoubtedly open new
and unique avenues in the %%%treatment%%% of %%%heart%%% %%%failure%%%.
Thus, it is expected that further studies using genetically engineered mouse models will not only continue to advance our understanding of the genetic regulation of cardiac function and dysfunction, but will also provide valuable insights into the development of therapeutic approaches to %%%treat%%% %%%heart%%% %%%failure%%%.

4/7/49 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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07460003 EMBASE No: 1998381441
Influences of increased expression of the Casup 2sup + ATPase of the sarcoplasmic reticulum by a transgenic approach on cardiac contractility
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Annals of the New York Academy of Sciences (ANN. NEW YORK ACAD. SCI.) (
United States) 1998, 853/- (43-48)
CODEN: ANYAA ISSN: 0077-8923
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 19

Congestive %%%heart%%% %%%failure%%% is a significant clinical problem
and leads to abnormalities in Casup 2sup + transients and to decreases in the level of the Casup 2sup + ATPase of the sarcoplasmic reticulum according to reports to some investigators. The Casup 2sup + ATPase of the sarcoplasmic reticulum (SERCA2) contributes in an important manner to diastolic Casup 2sup + lowering and relaxation of the %%%heart%%%. To determine the contractile alterations resulting from increased SERCA2 expression, we generated transgenic mice overexpressing a rat SERCA2 transgene. In these mice, SERCA2 mRNA was increased 2.6-fold, the relative
synthesis rate of SERCA2 protein 1.8-fold, and SERCA2 protein levels 1.2-fold. Functional analysis of Casup 2sup + handling and contractile parameters in isolated cardiac myocytes indicated that the intracellular Casup 2sup + decline and myocyte relengthening were each accelerated by 22-23%. In addition, studies in isolated papillary muscles showed that the time to half-maximal post-rest potentiation was significantly shorter, hinting at an increased Casup 2sup + loading of the sarcoplasmic reticulum. Furthermore, in vivo cardiac functional studies demonstrated a significant accelerated contraction and relaxation in SERCA2 transgenic mice. We also cloned a SERCA2 transgene and mutants of the %%%phospholamban%%% gene into
E1 deleted replication-deficient human adenovirus 5 viral vectors and infected cardiac myocytes. In the cardiac myocytes, endogenous SERCA2 levels were decreased by PMA %%%treatment%%%. Infection of such myocytes
with a SERCA2 expressing adenovirus could reconstitute the Casup 2sup + transient, and augmented oxalate facilitated SERCA2 Casup 2sup + uptake. In
addition, %%%phospholamban%%% mutants with changes of basic to acidic amino
acids in the cytoplasmic domain increased SERCA2 activity by 30-35%. These
findings, therefore, suggest that increased SERCA2 activity can be achieved by increasing SERCA2 levels or by expressing %%%phospholamban%%% mutants.
Increased SERCA2 activity can lead to significant enhancements of Casup 2sup + transients and myocardial contractility.

4/7/50 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
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07341272 EMBASE No: 1998245552
Remodeling of cardiac membranes during the development of congestive %%%heart%%% %%%failure%%%
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Dr. N.S. Dhalla, Institute of Cardiovascular Sciences, St. Boniface Gen. Hosp. Res. Center, 351 Tache Avenue, Winnipeg, Man. R2H 2A6 Canada
Heart Failure Reviews (HEART FAIL. REV.) (Netherlands) 1998, 2/4 (261-272)
CODEN: HFREF ISSN: 1382-4147
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

NUMBER OF REFERENCES: 125

Various proteins such as Casup 2sup + channels, Casup 2sup +-pump ATPase, Nasup +- Casup 2sup + exchanger, and Nasup +-Ksup + ATPase in the sarcolemmal (SL) membrane are considered to be intimately involved in Casup 2sup +-influx and Casup 2sup +-efflux processes in the cardiomyocyte. On the other hand, Casup 2sup +-pump ATPase, Casup 2sup +-release channels, Casup 2sup +-regulatory protein (%%%phospholamban%%%), and Casup 2sup +-binding protein (calsequestrin) in the sarcoplasmic reticulum (SR) are known to participate in raising and lowering the intracellular concentration of Casup 2sup + for the occurrence of cardiac contraction and relaxation processes. Therefore, a defect in any of the SL and SR proteins can be seen to result in Casup 2sup +-handling abnormalities in cardiomyocytes and subsequently in cardiac dysfunction during the development of %%%heart%%% %%%failure%%%. In this review, evidence is presented to show that changes in the expression of genes specific for cardiac membrane proteins may lead to remodeling of both SR and SL membranes during the development of %%%heart%%% %%%failure%%%. Although a
great deal of work on changes in gene expression for the SR membrane proteins has been carried out in the failing %%%heart%%%, relatively little information regarding changes in gene expression for SL proteins has appeared in the literature. Prevention of remodeling of cardiac membranes by modification of changes in the gene expression is suggested to serve as an important target for the %%%treatment%%% of %%%heart%%% %%%failure%%%.

4/7/51 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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07101537 EMBASE No: 1997383401
Injury to the Casup 2sup + ATPase of the sarcoplasmic reticulum in anesthetized dogs contributes to myocardial reperfusion injury
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Cardiovascular Research (CARDIOVASC. RES.) (Netherlands) 1997, 36/2 (174-184)
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PUBLISHER ITEM IDENTIFIER: S0008636397001752
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 50

Objective: Sarcoplasmic reticulum dysfunction may contribute to calcium (Casup 2sup +) overload during myocardial reperfusion. The aim of this study was to investigate its role in reperfusion injury. Methods: Open chest dogs undergoing 15 min of left anterior descending coronary artery occlusion and 3 h of reperfusion were randomized to intracoronary infusions of 0.9% saline, vehicle, or the Casup 2sup + channel antagonist, nifedipine (50 mug/min from 2 minutes before to 5 minutes after reperfusion). After each experiment, transmural myocardial biopsies were removed from ischemic/reperfused and nonischemic myocardium in the beating state and analyzed for (i) sarcoplasmic reticulum protein content (Casup 2sup + ATPase, %%%phospholamban%%%, and calsequestrin) by immunoblotting and (ii)
Casup 2sup + uptake by sarcoplasmic reticulum vesicles with and without 300 micromolar ryanodine or the Casup 2sup + ATPase activator, antiphospholamban (2D12) antibody. Results: Contractile function did not recover in controls and vehicle-%%%treated%%% dogs after ischemia and reperfusion (mean systolic shortening, -2 +/- 2%), but completely recovered in nifedipine- %%%treated%%% dogs (17 +/- 2%, p = NS vs. baseline, p < 0.01 vs. control). Ventricular fibrillation occurred in 50% of controls and vehicle dogs and 0% of nifedipine-%%%treated%%% dogs (p < 0.01). Casup 2sup
+ uptake by the sarcoplasmic reticulum vesicles was severely reduced in ischemic/reperfused myocardium of controls and vehicle dogs (p < 0.01 vs. nonischemic). Ryanodine and the 2D12 antibody improved, but did not reverse
the low Casup 2sup + uptake. Protein content was similar in ischemic/reperfused and nonischemic myocardium. In contrast, Casup 2sup + uptake and the responses to ryanodine and 2D12 antibody were normal in ischemic/reperfused myocardium from nifedipine-%%%treated%%% dogs. Conclusion: Dysfunction of the sarcoplasmic reticulum Casup 2sup + ATPase pump correlates with reperfusion injury. Reactivation of Casup 2sup + channels at reperfusion contributed to Casup 2sup + pump dysfunction. Casup 2sup + pump injury may be a critical event in myocardial reperfusion injury.

4/7/52 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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06256039 EMBASE No: 1995292198
Cyclic gmp-mediated %%%phospholamban%%% phosphorylation in intact cardiomyocytes
Sabine B.; Willenbrock R.; Haase H.; Karczewski P.; Wallukat G.; Dietz R. ; Krause E.-G.
Max Delbruck Ctr Molecular Medicine, Robert-Rossle Strasse 10,13122 Berlin Germany
Biochemical and Biophysical Research Communications (BIOCHEM. BIOPHYS.
RES. COMMUN.) (United States) 1995, 214/1 (75-80)
CODEN: BBRCA ISSN: 0006-291X
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The cGMP-mediated %%%phospholamban%%% phosphorylation was investigated in
cardiomyocytes in response to receptor-dependent (atrial natriuretic peptide, ANP) and -independent (sodium nitroprusside; SNP) cGMP generation.
ANP (InM-1muM) induced %%%phospholamban%%% phosphorylation in a concentration-dependent fashion (EC$D5inf 0: 5.0 +/- 0.09 nM). Concomitantly, an elevation in cGMP levels was observed.
%%%Phospholamban%%% was also dose-dependently phosphorylated in response to
SNP, but it required about three orders of magnitude higher concentrations (EC$D5inf 0: 2.9 +/- 0.03 muM) than ANP. %%%Treatment%%% of the cells with
8Br-cGMP (10 muM) or with the specific activator of cGMP-protein kinase 8-pCPT-cGMP (1-100 muM) mimicked these effects. The results demonstrate for
the first time that a ANP/cGMP signaling pathway exists in neonatal cardiomyocytes which may contribute to modulation of %%%heart%%% contractility.

4/7/53 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE
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06098698 EMBASE No: 1995129331
Endothelin-1 does not phosphorylate %%%phospholamban%%% and troponin I in
intact beating rat hearts
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Department of Pharmacology, Hokkaido University, School of Medicine,Sapporo 060 Japan
European Journal of Pharmacology - Molecular Pharmacology Section (EUR. J. PHARMACOL. MOL. PHARMACOL. SECT.) (Netherlands) 1995, 289/2 (175-180)
CODEN: EJPPE ISSN: 0922-4106
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

To determine a role of phosphorylation of specific cardiac regulatory proteins in the positive inotropic effect of endothelin-1, we examined phosphorylation of sarcoplasmic reticulum and myofibrillar proteins in perfused beating rat hearts %%%treated%%% with endothelin-1. In parallel experiments, the effects of isoprenaline and phorbol-12,13-dibutyrate (PDB) on protein phosphorylation were also tested. In sup 3sup 2P(i)-labeled hearts, perfusion with isoprenaline (100 nM) caused 4.4- and 10.4-fold increases in the degree of phosphorylation of %%%phospholamban%%% in sarcoplasmic reticulum and of troponin I in myofibrils, respectively. In contrast, neither endothelin-1 (100 nM) nor PDB (muM) significantly changed the phosphorylation state of these proteins. These findings provide evidence that phosphorylation of major cardiac regulatory proteins is not

responsible for the positive inotropic action of endothelin-1.

4/7/54 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE

05989914 EMBASE No: 1995018525
Lusitropic effects of alpha- and beta-adrenergic stimulation in amphibian %%%heart%%%
Petroff M.V.; Mundina-Weilenmann C.; Vittone L.; De Cingolani G.C.; Mattiazzi A.
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Molecular and Cellular Biochemistry (MOL. CELL. BIOCHEM.) (United States) 1994, 141/2 (87-95)
CODEN: MCBIB ISSN: 0300-8177
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The effects of beta and alpha-adrenergic stimulation in amphibian superfused hearts and ventricular strips were studied. Superfusion with 3 x 10sup -sup 8 M isoproterenol produced a positive inotropic effect, as detected by a 92 +/- 24% increase in the maximal rate of contraction (+T) and a positive lusitropic effect characterized by a decrease in both the ratio +T/-T (23 +/- 5%) and the half relaxation time (t(1/2)) (19 +/- 4%). The mechanical behavior induced by the beta-agonist was associated With an
increase in the intracellular cAMP levels from control values of 173 +/- 19 to 329 +/- 28 nmol/mg wet tissue. Hearts superfused with sup 3sup 2P in the
presence of isoproterenol showed a significant increase in Tn 1 phosphorylation (from 151 +/- 13 to 240 +/- 44 pmol sup 3sup 2P/mg MF protein) without consistent changes in phosphorylation of C-protein. In sarcoplasmic reticulum membrane vesicles, no %%%phospholamban%%% phosphorylation was detected either by beta-adrenergic stimulation of superfused hearts or when phosphorylation conditions were optimized by direct %%%treatment%%% of the vesicles with cAMP-dependent protein kinase
(PKA) and (y sup 3sup 2P) ATP. The effect of alpha-adrenergic stimulation on ventricular strips was studied at 30 and 22degreeC. At 30degreeC, the effects of 10sup - sup 5 to 10sup -sup 4M phenylephrine on myocardial contraction and relaxation were diminished to non significant levels by addition of propranolol. At 22degreeC, blockage with propranolol left a remanent positive inotropic effect (10% of the total effect of phenylephrine) and changed the phenylephrine-induced positive lusitropic effect into a negative lusitropic action. These propranolol-resistant effects were abolished by prazosin. Our results suggest that in amphibian %%%heart%%%, both the inotropic and lusitropic responses to catecholamines
are mainly due to a beta-adrenergic stimulation which predominates over the alpha-adrenergic response. %%%Phospholamban%%% phosphorylation seems not to
be involved in mediating the positive lusitropic effect of beta- adrenergic agents whereas phosphorylation of troponin I may play a critical role.

4/7/55 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE

04469907 EMBASE No: 1990358016
Effect of chlordecone (Kepone ((R))) on calcium transport mechanisms in rat %%%heart%%% sarcoplasmic reticulum
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Department of Neurology, University of Mississippi Medical Center, Jackson, MS 39216 United States
Pharmacology and Toxicology (PHARMACOL. TOXICOL.) (Denmark) 1990, 67/3
(227-234)
CODEN: PHTOE ISSN: 0901-9928
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LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Previous studies from our laboratory have indicated that chlordecone (Kepone ((R)), CD), an organochlorine insecticide, inhibited cardiac sodium pump activity and catecholamine uptake suggesting that CD may interfere with cardiac function. Sarcoplasmic reticulum (SR) calcium pump has an important role in myocardial contraction and relaxation, besides Nasup + transport. Since CD interferes with cardiac Nasup + ion translocases, we have studied CD effects on cardiac SR calcium pump activity. Experiments were carried out both in vitro and in vivo. SR was isolated from %%%heart%%% ventricles of male Sprague-Dawley rats. Cardiac SR Casup 2sup
+-ATPase, sup 4sup 5Ca-uptake and cAMP as well as calmodulin (CaM) dependent protein phosphorylation were measured. Casup 2sup +-ATPase was differentiated into low affinity and high affinity forms by measuring the activity using 50 and 0.7 muM free Casup 2sup + respectively. CD in vitro inhibited sup 4sup 5Ca-uptake by SR in a concentration dependent manner with an IC50 value of 7 muM and SR sup 4sup 5Ca-uptake was totally inhibited at 20-30 muM CD. In agreement with this, both high affinity and low affinity Casup 2sup +-ATPases, which are involved in Casup 2sup + transport across membranes, were also inhibited by CD in a concentration dependent manner with IC50 values of 0.7 and 3.2 muM respectively. Both Casup 2sup +-ATPase and sup 4sup 5Ca-uptake by cardiac SR were significantly lower in rats %%%treated%%% with CD (25, 50 or 75 mg/kg) when
compared to control rats. cAMP as well as CaM significantly elevated the sup 3sup 2P-binding to SR proteins in vitro to about 70-80%. In the presence of CD, this sup 3sup 2P-binding was reduced, however, not concentration dependent. In agreement with in vitro studies, sup 3sup 2P-bound to proteins was significantly lowered in rats %%%treated%%% with
CD. SDS-polyacrylamide gel electrophoresis of the cardiac SR revealed the presence of at least 30 comassie blue-stainable bands with mobilities corresponding to molecular weights ranging from 9 to 120 kDa using 15% acrylamide gels. Autoradiographs from samples incubated in the presence of cAMP or CaM indicated sup 3sup 2P-incorporation in 7 bands. Of these, bands
corresponding to about 24 kDa and adjacent lower molecular weights decreased in their intensity by CD in vitro as well as in vivo. These results indicate that CD %%%treatment%%% may be reducing SR calcium transport mechanisms by altering phosphorylation of a number of proteins including %%%phospholamban%%% in rat cardiac SR.

4/7/56 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE

04360382 EMBASE No: 1990248446
%%%Phospholamban%%% and troponin I are substrates for protein kinase C in
vitro but not in intact beating guinea pig hearts
Edes I.; Kranias E.G.
Dept. Pharmacol./Cell Biophys., University of Cincinnati, College of Medicine,Cincinnati, OH 45267-0575 United States
Circulation Research (CIRC. RES.) (United States) 1990, 67/2 (394-400)
CODEN: CIRUA ISSN: 0009-7330
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The incorporation of (sup 3sup 2P)inorganic phosphate into membranous, myofibrillar, and cytosolic proteins was studied in Langendorff-perfused guinea pig hearts %%%treated%%% with phorbol 12-myristate 13-acetate (PMA)
or 1,2-dioctanoylglycerol (D8G), which are potent activators of protein kinase C. Control hearts were perfused with an inactive phorbol ester (4alpha-phorbol 12,13-didecanoate), which does not cause activation of protein kinase C. To ensure the blockade of different receptor systems, the perfusions were carried out in the presence of prazosin, propranolol, and atropine. Perfusion of hearts with either PMA (4 muM) or D8G (200 muM) was
associated with a negative effect on left ventricular inotropy and relaxation. Examination of the sup 3sup 2P incorporation into various fractions revealed that there were no increases in the degree of phosphorylation of %%%phospholamban%%% in sarcoplasmic reticulum, and troponin I and C protein in the myofibrils, although these proteins were found to be substrates for protein kinase C in vitro. However, in the same hearts, there were significant changes in the sup 3sup 2P incorporation into a 28-kDa cytosolic protein. Examination of the activity levels of protein kinase C in hearts perfused with PMA indicated a redistribution of

this activity from the cytosolic to the membrane fraction, suggesting the activation of the enzyme in vivo. These findings indicate that regulatory phosphoproteins, which may be phosphorylated by protein kinase C in vitro, are not substrates for protein kinase C in beating hearts perfused with phorbol esters or diacylglycerol analogues.

4/7/57 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE

03943704 EMBASE No: 1989112697
Regulation of myocardial Casup 2sup +-ATPase and %%%phospholamban%%% mRNA
expression in response to pressure overload and thyroid hormone
Nagai R.; Zarain-Herzberg A.; Brandl C.J.; Fujii J.; Tada M.; MacLennan D.H.; Alpert N.R.; Periasamy M.
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The sarcoplasmic reticulum (SR) and the contractile protein myosin play an important role in myocardial perfomance. Both of these systems exhibit plasticity - i.e., quantitative and/or qualitative reorganization during development and in response to stress. Recent studies indicate that SR Casup 2sup + uptake function is altered in adaptive cardiac hypertrophy and %%%failure%%%. The molecular basis (genetic and phenotypic) for these changes is not understood. In an effort to determine the underlying causes of these changes, we characterized the rabbit cardiac Casup 2sup +-ATPase phenotype by molecular cloning and ribonuclease A mapping analysis. Our results show that the %%%heart%%% muscle expresses only the slow-twitch SR
Casup 2sup +-ATPase isoform. Second, we quantitated the steady-state mRNA
levels of two major SR Casup 2sup + regulatory proteins, the Casup 2sup +-ATPase and %%%phospholamban%%%, to see whether changes in mRNA content
might provide insight into the basis for functional modification in the SR of hypertrophied hearts. In response to pressure overload hypertrophy, the relative level of the slow-twitch/cardiac SR Casup 2sup +-ATPase mRNA was decreased to 34% of control at 1 week. The relative Casup 2sup +-ATPase mRNA level increased to 167% of control after 3 days of %%%treatment%%%
with thyroid hormone. In contrast, in hypothyroid animals, the relative Casup 2sup +-ATPase mRNA level decreased to 51% of control at 2 weeks. The
relative level of %%%phospholamban%%% mRNA was decreased to 36% in 1-week
pressure overload. Hyperthyroidism induced a decrease to 61% in the %%%phospholamban%%% mRNA level after 3 days of %%%treatment%%%, while
hypothyroidism has virtually no effect on %%%phospholamban%%% mRNA levels.
These data indicate that the expression of SR Casup 2sup +-ATPase and %%%phospholamban%%% mRNA may not be coordinately regulated during myocardial adaptation to different physiological conditions.

4/7/58 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE

03818976 EMBASE No: 1988268416
The effects of Bay K 8644 on myocardial relaxation and cAMP levels in perfused rat %%%heart%%%: Role of sympathetic neurotransmitter release
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Journal of Molecular and Cellular Cardiology (J. MOL. CELL. CARDIOL.) (United Kingdom) 1988, 20/9 (765-769)
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Bay K 8544 typifies a number of drugs known to act directly on voltage-dependent calcium channels to increase calcium current. Such effects probably underly the drug's positive inotropic action and smooth muscle stimulation. Although the effects of this compound on myocardial contractility have been extensively described, its action upon myocardial relaxation is not well established. Either no changes or a prolongation in ventricular relaxation have been mentioned. On the other hand, during the course of other experiments performed in our laboratory with the perfused rat %%%heart%%% (unpublished results), we observed that Bay K 8644 elicits
a moderate but consistent relaxant effect. The present work was undertaken
in an attempt to clarify the effect of Bay K 8644 upon myocardial relaxation. Evidence will be presented showing that in the perfused rat %%%heart%%%, the positive inotropic action of Bay K 8644 occurs together with a prolongation of the contraction time (TTP) without changes in time to half relaxation (t1/2). However, an enhancement of ventricular relaxation was detected by the proportional greater increase in maximal velocity of relaxation (-T.) with respect to maximal velocity of contraction (+T.) and the shortening of the time constant of relaxation (tau). These actions occur associated with a significant increase in cAMP levels and %%%phospholamban%%% phosphorylation. Either the relaxant effect
as well as the increments in cAMP and %%%phospholamban%%% phosphorylation
were abolished when the hearts were depleted of norepinephrine by previous %%%treatment%%% with reserpine. Depletion of norepinephrine stores also decreases the positive inotropic effect of the drug. These results strongly suggest that Bay K 8644, besides its direct action upon the myocardial cell, evokes a release of neurotransmitter norepinephrine from sympathetic nerve terminals of the %%%heart%%%. This release may partially account for
the inotropic action of the drug and fully explain the relaxant effect elicited by this compound in the perfused rat %%%heart%%%.

4/7/59 (Item 16 from file: 73)
DIALOG(R)File 73:EMBASE

03570860 EMBASE No: 1988020296
%%%Phospholamban%%% stoichiometry in canine cardiac muscle sarcoplasmic
reticulum
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Neurochemical Research (NEUROCHEM. RES.) (United States) 1987, 12/10
(937-941)
CODEN: NERED ISSN: 0364-3190
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

%%%Treatment%%% of cardiac sarcoplasmic reticulum with the crosslinking
reagent dithiobis (succinimidyl propionate) in the presence of sup 1sup 2sup 5I-calmodulin, resulted in the formation of a 40,000-dalton affinity labeled component, consisting of a 1:1, %%%phospholamban%%%: sup 1sup 2sup
5I-calmodulin complex. In parallel experiments, sarcoplasmic reticulum was phosphorylated in the presence of calmodulin and (gamma-sup 3sup 2P)ATP, and then %%%treated%%% with the crosslinking reagent to produce an affinity
labeled component consisting of a 1:1, calmodulin: sup 3sup 2P-%%%phospholamban%%% complex. These experiments permitted determination of
the amount of sup 1sup 2sup 5I and sup 3sup 2P incorporated into the 40,000-dalton complexes, as well as the amount of sup 3sup 2P incorporated into the 23,000-dalton form of %%%phospholamban%%%. If 1 mol of Casup 2sup
+-dependent ATPase phosphoprotein represents 1 mol of 100,000-dalton Casup

2sup +-dependent ATPase monomer, then there are 4.88 +/- 1.33 mol Casup 2sup +-dependent ATPase/mol of phospholamba. If there are 2 mol of Casup 2sup +-dependent ATPase phosphoprotein/mol of 100,000-dalton Casup 2sup +-dependent ATPase monomer, then there are 9.76 +/- 2.66 mol Casup 2sup +-dependent ATPase/mol %%%phospholamban%%%.

4/7/60 (Item 17 from file: 73)
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03289732 EMBASE No: 1986042309
Identification of an endogenous protein kinase C activity and its intrinsic 15-kilodalton substrate in purified canine cardiac sarcolemmal vesicles
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Department of Medicine, Indiana University School of Medicine, Indianapolis, IN 46202 United States
Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1985, 260/25 (13879-13889)
CODEN: JBCHA
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

The cardiac sarcolemmal 15-kDa protein, previously shown to be the principal sarcolemmal substrate phosphorylated in intact %%%heart%%% in response to beta-adrenergic stimulation, was demonstrated to be the major substrate phosphorylated in purified canine cardiac sarcolemmal vesicles by an intrinsic protein kinase C activity. The intrinsic protein kinase C, detected by its ability to phosphorylate H1 histones, was most concentrated in cardiac sarcolemmal vesicles and absent from sarcoplasmic reticulum membranes. Unmasking techniques localized the intrinsic protein kinase activity and its principal endogenous substrate, the 15-kDa protein, to the cytoplasmic surfaces of sarcolemmal vesicles; %%%phospholamban%%% contaminating the sarcolemmal preparation was not significantly phosphorylated. The intrinsic protein kinase C required micromolar Casup 2sup + for activity, but not calmodulin. Half-maximal phosphorylation of the 15-kDa protein occurred at 10 muM Casup 2sup +; optimal phosphorylation
of the 15-kDa protein by protein kinase C and Casup 2sup + was additive to that produced by cAMP-dependent protein kinase. Exogenous phospholipids were not required to activate endogenous protein kinase C. However, heat-%%%treated%%% sarcolemmal vesicles, in which intrinsic protein kinase activities were inactivated, were sufficient to maximally activate soluble protein kinase C prepared from rat brain, suggesting that all the necessary phospholipid cofactors were already present in sarcolemmal vesicles. Of the many proteins present in sarcolemmal vesicles, only the 15-kDa protein was phosphorylated significantly in heat-inactivated sarcolemmal vesicles by soluble protein kinase C, confirming that the 15-kDa protein was a preferential substrate for this enzyme. Consistent with a protein kinase C activity in sarcolemmal vesicles, the tumor-promoting phorbol ester 12-O-tetradecanoylphorbol 13-acetate stimulated 15-kDa protein phosphorylation severalfold, producing approximately 70% of the maximal phosphorylation even in the absence of significant ionized Casup 2sup +. The results are compatible with an intrinsic protein kinase C activity in sarcolemmal vesicles whose major substrate is the 15-kDa protein.

4/7/61 (Item 18 from file: 73)
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03146539 EMBASE No: 1986169116
Characterization of the membrane-bound protein kinase C and its substrate proteins in canine cardiac sarcolemma
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Biochimica et Biophysica Acta - Molecular Cell Research (BIOCHIM. BIOPHYS. ACTA MOL. CELL RES.) (Netherlands) 1986, 886/1 (152-161)
CODEN: BAMRD
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Cardiac sarcolemma was purified from canine ventricles. Enrichment of the sarcolemmal membranes was demonstrated by the high (Nasup + + Ksup +)-ATPase activity of 28.0 +/- 1.5 mumol P(i)/mg protein per h and the high concentration of muscarinic receptors with the B(max) of 8.2 +/- 2.5 pmol/mg protein as determined by (sup 3H)QNB binding. The purified sarcolemma also contains significant levels of a membrane-bound Casup 2sup + and phospholipid-dependent protein kinase (protein kinase C). To elucidate the protein kinase C activity in sarcolemma, a prior incubation of the membranes with EGTA and Triton X-100 was necessary. The specific activity of protein kinase C was found to be 131.4 pmol P(i)/mg per min, in the presence of 6.25 mug phosphatidylserine and 0.5 mM CaClinf 2. %%%Treatment%%% of sarcolemma with 12-O-tetradecanoylphorbol 13-acetate
(TPA) and phorbol 12,13-dibutyrate (PBuinf 2) resulted in a concentration-dependent activation of protein kinase C activity. The effect of TPA and PBuinf 2 on protein kinase C in sarcolemma was independent of exogenous Casup 2sup + and phosphatidylserine. Polymyxin B inhibited phorbol-ester-induced activation of protein kinase C activity. The distribution of protein kinase C in the cytosolic fraction was also examined. The specific activity of the kinase in the cytosolic fraction was 59.7 pmol P(i)/mg per min. However, the total protein kinase C activity in the cytosol was 213500 pmol P(i)/min, compared to that of 1025 pmol P(i)/min in the sarcolemma isolated from approx. 100 g of canine ventricular muscle. Several endogenous proteins in cardiac sarcolemma were phosphorylated in the presence of Casup 2sup + and phosphatidylserine. The major substrates for protein kinase C were proteins of M(r) 94000, 87000, 78000, 51000, 46000, 11500 and 10000. Most of these substrate proteins have
not been identified before. Other proteins of M(r) 38000, 31000 and 15000 were markedly phosphorylated in the presence of Casup 2sup + only. Phosphorylation of %%%phospholamban%%% (M(r) 27000 and 11000) was also
stimulated in the presence of Casup 2sup + and phosphatidylserine, but the low M(r) form of %%%phospholamban%%% was distinct from two other low M(r)
substrate proteins for protein kinase C. Polymyxin B was more selective in inhibiting the protein kinase C dependent phosphorylation. On the other hand, trifluoperazine selectively inhibited the phosphorylation of %%%phospholamban%%% and an M(r) 150000 protein. Although the exact function
of this kinase is unknown, based on these observation, we believe that protein kinase C in the cardiac sarcolemma may play an important role in the cell-surface-signal regulated cardiac function.

4/7/62 (Item 19 from file: 73)
DIALOG(R)File 73:EMBASE
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02943332 EMBASE No: 1985087291
Regulation of Casup 2sup +-transport by cyclic 3',5'-AMP-dependent and calcium-calmodulin-dependent phosphorylation of cardiac sarcoplasmic reticulum
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Biochimica et Biophysica Acta - Molecular Cell Research (BIOCHIM. BIOPHYS. ACTA MOL. CELL RES.) (Netherlands) 1985, 844/2 (193-199)
CODEN: BAMRD
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Canine cardiac sarcoplasmic reticulum is phosphorylated by cyclic AMP-dependent and by Casup 2sup +-calmodulin-dependent protein kinase on a
22 kDa protein, called %%%phospholamban%%%. Both types of phosphorylation
have been shown to stimulate the initial rates of Casup 2sup + transport. To establish the interrelationship of the cAMP-dependent and Casup 2sup +-calmodulin-dependent phosphorylation on Casup 2sup + transport, cardiac sarcoplasmic reticulum vesicles were preincubated under optimum conditions for: (a) cAMP-dependent phosphorylation, (b) Casup 2sup +-calmodulin-dependent phosphorylation, and (c) combined cAMP-dependent and
Casup 2sup +-calmodulin-dependent phosphorylation. Control vesicles were %%%treated%%% under identical conditions, but in the absence of ATP, to avoid phosphorylation. Control and phosphorylated sarcoplasmic reticulum vesicles were subsequently centrifuged and assayed for Casup 2sup +

transport in the presence of 2.5 mM Tris-oxalate. Our results indicate that cAMP-dependent and Casup 2sup +-calmodulin-dependent phosphorylation can
each stimulate calcium transport in an independent manner and when both are
operating, they appear to have an additive effect. Stimulation of Casup 2sup + transport was associated with a statistically significant increase in the apparent affinity for calcium by each type of phosphorylation. The degree of stimulation of the calcium affinity was relatively proportional to the degree of %%%phospholamban%%% phosphorylation. These findings suggest the presence of a dual control system which may operate in independent and combined manners for regulating cardiac sarcoplasmic reticulum function.

4/7/63 (Item 20 from file: 73)
DIALOG(R)File 73:EMBASE

01405310 EMBASE No: 1979126084
Enhanced phosphorylation of myocardial sarcoplasmic reticulum in experimental hyperthyroidism
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Cardiovasc. Div., Dept. Med., Univ. Minnesota Med. Sch., Minneapolis, Minn. 55455 United States
American Journal of Physiology - Heart and Circulatory Physiology (AM. J. PHYSIOL. HEART CIRC. PHYSIOL.) (United States) 1978, 3/4 (H426-H431)
CODEN: AJPPD
DOCUMENT TYPE: Journal
LANGUAGE: ENGLISH

Calcium transport by cardiac sarcoplasmic reticulum (SR) was compared in hyperthyroid (HT) and euthyroid (ET) rats. Both Casup 2sup + uptake (97 +/- 3.1 nmol/mg per min in HT vs. 63 +/- 2.9 nmol/mg per min in ET, P < 0.01) and Casup 2sup +-stimulated ATPase activity (61 +/- 4.1 vs. 37 +/- 1.6 nmol/ P(i)/mg per min, P < 0.01) were higher in the thyroxine-%%%treated%%%
animals. These changes were accompanied by enhanced cyclic AMP-dependent
phosphorylation of cardiac SR in hyperthyroid rats (180 +/- 4.3 pmol P(i)/mg per min vs. 117 +/- 4.2 pmol P(i)/mg per min, P < 0.01). SDS polyacrylamide gel electrophoresis of cardiac SR showed that phosphorylation of a 22,000-dalton protein (%%%phospholamban%%%) primarily
accounted for the differences between the 2 groups. There was no difference
in the rate of SR dephosphorylation by endogenous phosphoprotein phosphatase between HT and ET rats. Differences in cyclic AMP-dependent phosphorylation between the 2 groups were blunted in the presence of excess
exogenous cyclic AMP-dependent protein kinase. These results suggest that increased levels or activity of endogenous cyclic AMP-dependent protein kinases may partially explain enhanced calcium transport by the cardiac SR of hyperthyroid animals.

4/7/64 (Item 1 from file: 98)
DIALOG(R)File 98:General Sci Abs/Full-Text

04014400 H.W. WILSON RECORD NUMBER: BGSI99014400 (THIS IS THE FULLTEXT)
Myoblast cell grafting into %%%heart%%% muscle: cellular biology and potential applications.
AUGMENTED TITLE: review
Kessler, P. D
Byrne, B. J
Annual Review of Physiology (Annu Rev Physiol) v. 61 ('99) p. 219-42
LANGUAGE: English
COUNTRY OF PUBLICATION: United States
WORD COUNT: 11875

ABSTRACT: This review surveys a wide range of cellular and molecular approaches to strengthening the injured or weakened %%%heart%%%, focusing
on strategies to replace dysfunctional, necrotic, or apoptotic cardiomyocytes with new cells of mesodermal origin. A variety of cell types, including myogenic cell lines, adult skeletal myoblasts, immortalized atrial cells, embryonic and adult cardiomyocytes, embryonic stem cells, teratoma cells, genetically altered fibroblasts, smooth muscle cells, and bone marrow-derived cells have all been proposed as useful cells in cardiac repair and may have the capacity to perform cardiac work. We focus on the implantation of mesodermally derived cells, the best developed of the options. We review the developmental and cell biology that have stimulated these studies, examine the limitations of current knowledge, and identify challenges for the future, which we believe are considerable. With permission, from the Annual Review of Physiology, Volume 61, 1999, by Annual Reviews Inc. (http://www.annurev.org).

TEXT:
KEY WORDS: skeletal muscle, cardiomyocytes, cell transplantation, cardiac regeneration, transdifferentiation

INTRODUCTION
Techniques that introduce new myogenic cells into the %%%heart%%%, induce
the replication of myocardial cells in situ, or allow cells resident in the %%%heart%%% to convert to a myogenic phenotype have great potential for %%%treating%%% %%%heart%%% %%%failure%%% and cardiomyopathy. The ultimate
goal of this work is to repair, replace, or enhance the biological function of damaged cells in order to strengthen the weakened %%%heart%%%. Cell implantation may also provide a "platform" for the stable local delivery of recombinant proteins.

These studies have been an active area of investigation since the introduction of exogenous cells in canine %%%heart%%% was first reported (1). These investigators demonstrated the successful grafting and subsequent myodifferentiation of autologous canine myoblasts (satellite cells) in canine cryoinjury (1, 2). Subsequent investigations utilized immortalized myogenic cells in rodents (3-5). A concern that skeletal muscle cells could not appropriately communicate with the underlying myocardium (a matter of some controversy) led to an extension of this approach to fetal cardiomyocyte grafts, which form intercalated disks and gap junctions with native myocardium (6, 7).

Alternate approaches to generating cardiac substitutes have utilized immortalized atrial cell lines (8), and genetically selected embryonic stem cells (9). Alternative cell sources have been considered, including smooth muscle cells, bone marrow-derived cells, and embryonal carcinoma cells (10-13). Other strategies have focused on inducing undamaged cardiomyocytes
to replicate or identify "cardiogenic master genes" that might program a cell present in the %%%heart%%% (fibroblasts, smooth muscle, or endothelial
cells) or grafted cells (e.g. fibroblasts or myoblasts) to convert into cardiomyocytes. The goal of each of these interventions is to generate a cell that can perform cardiac work, respond appropriately to adjacent cardiomyocytes and nonmyocyte cells, and exhibit a favorable response to physiological and pathophysiological stimuli. Successful cardiac tissue engineering would provide a valuable alternative therapy for end-stage %%%heart%%% %%%failure%%% (reviewed in 14).

CONGESTIVE %%%HEART%%% %%%FAILURE%%%
Why develop cell transplantation for %%%heart%%% %%%disease%%%? Loss and
dysfunction of cardiomyocytes are characteristics of chronic %%%heart%%%
%%%disease%%%, including ischemic %%%heart%%% %%%disease%%%, hypertensive
%%%heart%%% %%%disease%%%, and idiopathic cardiomyopathy. These deficits in
cardiomycyte number lead to %%%heart%%% %%%failure%%%, which is a consequence of either primary or secondary irreversible cell loss. The molecular basis for the syndrome of congestive %%%heart%%%
%%%failure%%% is
a lack of stem cells in the %%%heart%%% and the inability of the damaged %%%heart%%% cells to undergo repair or divide (15-17). Cell transplantation strategies have been designed to replace damaged cells with cells that can perform cardiac work.

There is a pressing need for novel therapies to %%%treat%%%

%%%heart%%% %%%failure%%% (18). This condition affects an estimated 4.8
million Americans, and 400,000 new cases are diagnosed each year. The use of angiotensin-converting enzyme inhibitors and of beta-adrenergic blockers has improved survival in these patients (19-21). Additionally, new mechanical-assist devices, experimental surgical procedures, and xenotransplantation approaches are currently being developed (22-25), yet mortality remains high, with greater than 50[percent] of all patients succumbing within 5 years of initial diagnosis (26). The utility of cardiac transplantation is limited by a shortage of donor hearts, the complications of immunosuppression, and the %%%failure%%% of grafted organs. The idea of
transplanting single cells instead of entire organs has a number of attractive attributes and is dependent on an ever-expanding understanding of the molecular basis of skeletal myogenesis and early events in cardiogenesis, which are briefly reviewed below.

DEVELOPMENTAL AND CELL BIOLOGY

STEM CELLS

Mammalian embryos consist of pluripotent cells that have the capacity to form an entire organism. This capability of forming multiple cell lineages becomes progressively restricted with development, through a process known
as determination. Determined stem cells give rise to cells of a specific lineage (e.g. pluripotent hematopoetic progenitor cells give rise to various blood lineages), whereas committed progenitor cells (e.g. myoblasts or embryonic cardiomyocytes) have a more limited fate. The subsequent differentiation of committed cells can occur autonomously, without environmental influence.

Vertebrates respond to injury though activation of committed progenitor cells or stem cells (e.g. bone marrow) or through proliferation of differentiated cells (liver or endothelial cells) (reviewed in 27, 28). In skeletal muscle, committed progenitor cells (adult myoblasts, satellite cells) located below the basal lamina are induced to proliferate in response to injury (29). Skeletal muscle development or repair occurs along an orderly pathway, with commitment of stem cells to myogenic lineage (myoblasts), proliferation of myoblasts, and fusion of myoblasts to form myotubes. In the mammalian %%%heart%%%, a population of self-renewing cells
(stem cells) is not present, and there is compelling evidence that the proliferative capacity of adult cardiomyocytes is limited (15, 16, 30), although dissenting views have been presented (31). Following injury or infarction, there is no evidence of DNA synthesis (15). In contrast, regeneration of %%%heart%%% tissue does occur in the amphibian axolotl (see
section on urodele amphibians below) (32, 33).

SKELETAL MYOGENESIS

Despite the obvious similarity of cardiac and skeletal muscle, both being striated muscle, there are fundamental differences between the two types of
tissues, including morphology, mechanism of excitation-contraction coupling, embryological origin, and response to injury. Skeletal myogenesis involves activation of muscle-specific gene expression and withdrawal from the cell cycle. Although proliferation and differentiation are mutually exclusive in skeletal myocytes, differentiated cardiomyocytes can proliferate up to birth (30).

The idea that a master regulator controls skeletal muscle myogenesis has its origin in the work of Holzer and coworkers (34-36). They observed that the nucleoside analogue bromodeoxyuridine (BrdU) reversibly inhibited myogenesis in vitro. The muscle differentiation gene myoD was identified by 5-azacytidine-induced hypomethylation experiments as the target that bound
BrdU (37, 38) and has led to the identification of the family of myogenic determination factor(s). Forced expression of members of this family has led to the activation of myogenesis in fibroblasts, chondrocytes, and mesenchymal stem cells (e.g. C3H10T1/2). This effect was able to cross embryonic borders: The ectopic expression of myogenic determination factor(s) in cells of ectodermal retinal pigment epithelial cells, keratinocytes (39) or endodermal lineage liver cells (40) led to differentiation into skeletal muscle. Similarly, conversion of nonmyogenic cells to a myogenic phenotype occurred following the expression of the transcription factor MEF2A, or of the 3' untranslated region of muscle tropomysin (41, 42). Additionally, coculture of fibroblasts with the myogenic cells leads to conversion of fibroblasts into differentiated cells (43). The identification of factors that direct cells to a skeletal muscle phenotype has demonstrated a high degree of plasticity in differentiated cells that had been previously unappreciated and leads to the possibility that a similar strategy might be adopted to convert nonmyocyte cells into cardiomyocytes. However, BrdU does not inhibit cardiac differentiation, and not suprisingly, attempts to identify a myoD homologue in %%%heart%%% have
not been successful (44).

FORMATION OF THE VERTEBRATE %%%HEART%%%

The components of the circulatory system, %%%heart%%%, blood vessels, and
blood cells are all of mesodermal origin. The formation of the %%%heart%%%
consists of two stages: (a) specification and differentiation of cardiomyocytes, and (b) formation of a mature, four-chambered %%%heart%%%
(morphogenesis). Readers should consult these excellent reviews for further details (45-48).

Cardiogenesis involves complex interactions with growth factors, intrinsic and extrinsic signaling molecules, and the cellular matrix. The primitive %%%heart%%% tube develops from two clusters of mesodermal cells
(anterior lateral plate mesoderm) that are organized in a bilaterally symmetric fashion as precardiac mesoderm in the gastrula stage (49). The endothelium of the %%%heart%%% is derived from a distinct population of cells, at the edge of the two cardiac fields (50). These precardiac fields are brought together in the midline after gastrulation to form a two-layered %%%heart%%% tube with endocardial and myocardial layers.

Mesodermal populations that give rise to the primitive %%%heart%%% are
influenced by inductive factors secreted by anterior endoderm. In Drosophila, mutations in a transforming growth factor (TGF)-b/bone morphogenic protein (BMP)-like molecule (decaplentaplegic) or the fibroblast growth factor (FGF) receptor (heartless) are associated with an absence of the dorsal vessel, the %%%heart%%% homologue (51, 52). Similarly, mutations in tinman, a homeobox gene, also lead to absence of the dorsal vessel (53). The anterior mesoderm in chicken gastrula-stage embryos undergoes cardiac differentiation following exposure to the TGF-b family members BMP-2 and BMP-4 (54), and posterior mesoderm (which is not
normally cardiogenic) can be converted to cardiogenic material by the combination of BMP2 and FGF4 (55). Although the precise signals and receptors have not been identified in most of these systems, these studies stress the role of instructive stimuli derived from the endoderm in the specification of cells that form the %%%heart%%% or define the dorsal-ventral coordinates of the cells that give rise to the %%%heart%%%.

The zinc-finger transcription factors GATA-4 and Nkx2.5, a vertebrate homologue of tinman, are both expressed in early cardiac progenitor cells (56, 57) and can induce the expression of cardiac genes. Neither of these transcription factors functions like the basic helix-loop-helix myogenic regulator, MyoD, to induce cardiogenesis. Ectopic expression of Nkx2.5 in murine embryonic mesenchymal cells (C3H10T1/2) does not lead to cardiac specification and cardiogenesis (58). Forced expression of Nkx2.5 in Xenopus and zebrafish embryos produces an increase in cell number in the developing %%%heart%%% and %%%heart%%% size (59), and the activation of
myosin heavy chain expression in ectopic cells has also been observed in zebrafish (60). Similarly, overexpression of the homeobox gene ladybird causes the hyperplasia of dorsal vessel precursors in Drosophila (61). Targeted disruption of Nkx-2.5 in mice and mutations in humans suggest partial redundancy within the Nk gene family (62, 63), further indicating that other members of the family may be identical to Drosophila tinman (64-66), responsible for the initial commitment to the cardiac lineage. Despite expression of GATA-4 in early cardiogenic regions, mice that contain a homozygous inactivation of this gene contain differentiated cardiomyocytes (67, 68). Similar genetic strategies in mice have led to the identification of an array of genes, some of which show unexpected involvement in the thickening of the vertebrate %%%heart%%%: neuregulin, N-myc, gp130, and transcription factor enhancer 1 (69-73).

These data suggest the existence of a vast array of regulatory proteins that have the potential to convert noncardiac cells into embryonic cardiac cells. The process will likely involve genetic information that is intrinsic to the mesodermal lineage and inductive signals from endoderm.

However, the lack of a permissive cell type for use in monitoring the conversion to the cardiac phenotype (e.g C3H10T1/2) and an apparent lack of
dominance of the cardiac phenotype in heterokaryons (74) have made it difficult to adapt the approach used by Davis et al (37). to screen these candidates for the cardiac master gene. Furthermore, the proteins that have
been implicated by their expression in early cardiogenic regions may assign mesenchymal cells to a cardiogenic lineage and may function relatively late in cardiogenesis. Alternatively, there may be not unique factors but a combination of factors, or a stochastic pattern of expression that occurs uniquely in early cardiac development.

APPROACHES TO AUGMENTING CELL NUMBER IN THE %%%HEART%%%

Given the lack of regenerative capacity in the mammalian %%%heart%%%, strategies have been proposed to augment cardiac cell numbers using autologous, allogeneic, xenogeneic, immortalized, or transdifferentiated cells. There is an important unanswered question with each strategy: How will the transplanted cells respond to physiological and pathophysiological stimuli?

TRANSDIFFERENTIATION

Transdifferentiation is a fascinating biological phenomenon with potential applications in cardiac tissue engineering see review by Brockes (75) . The process of transdifferentiation involves the conversion of a committed, differentiated, or specialized cell to another differentiated cell type with a distinctly different phenotype. The pre- and postdifferentiated state must be clearly identifiable and distinct, and there must be a relationship between precursor cells and their progeny. It has been suggested that a single switch in the commitment program is responsible for these changes in phenotype (75).

TRANSDIFFERENTIATION IN URODELE MUSCLE Urodele amphibians (including
newt and axolotl) are the only adult vertebrates capable of regenerating limbs. The animal heals the wound, cells beneath the epidermis dedifferentiate, and regeneration occurs by local formation of a growth zone (blastema) that proliferates to form a new limb (75, 76). Newt myotubes lack reserve cells, and the regeneration involves reversal of the differentiated state instead of recruitment of satellite cells. It has been suggested that the environment of the growth zone leads to destabilization of the differentiated state (75). Myotubes implanted beneath the site of transection are able to revert from multinucleate structures to give rise to mononucleate progeny. When newt myotubes are shifted to high serum, they
reenter the cell cycle, whereas in mammals (77), serum-induced cell cycle reentry occurs only in the retinoblastoma protein null mice (78). Although newt myotubes are not lacking in retinoblastoma protein, exposure to serum may lead to inactivation of the protein (77). In addition, innervation is important for limb regeneration because the denervated limb cannot initiate the process of regeneration (79). Cardiac regeneration occurs in newts, and it is possible that this ability was lost in higher vertebrates because of selective pressures (75). It would be an enormous advance if such a transformation could be engineered in mammals (32, 33, 80).

TRANSDIFFERENTIATION IN MAMMALIAN MUSCLE There are numerous examples
of transdifferentiation into and from muscle cells. The electric organs of fish transdifferentiate from muscle (81), and smooth muscle in the external musculature of the mouse esophagus transdifferentate to striated muscle (82). Expression of the adipogenic transcription factors PPARg and C/EBPa in murine G8 myoblasts blocks muscle differentiation and promotes adipocyte
differentiation (83). It is interesting to speculate that fat cells observed within the %%%heart%%% or skeletal muscle in obesity, mitochondrial myopathies, fatty right ventricle, and right ventricular dysplasia (84) may result from transdifferentiation.

POSSIBLE TARGETS FOR TRANSDIFFERENTIATION Smooth muscle cells,
endothelial cells, mesenchymal stem cells (see section on mesenchymal stem cells), and fibroblasts have a differing developmental origin and represent cell types that might be transdifferentiated into cells capable of performing work. By analogy to the studies of Choi et al (39) and Weintraub et al (40, 85), forced expression of MyoD was utilized to attempt to convert cardiac fibroblasts into skeletal myotubes in situ (86). Although skeletal myogenesis was initiated, myofibrillogenesis did not occur (86). Alternative cell types have not been tested to date, although it is informative that the skeletal muscle differentiation program is a fundamentally incompatible aspect of the cardiac phenotype because forced expression of myoD or myogenic regulatory factor (myf5) in transgenic animals results in cardiomyopathy or death (87, 88).

PROLIFERATION OF CARDIOMYOCTYES IN SITU

Reversal of the terminal differentiation of uninjured cardiomyocytes represents an additional strategy for manipulating the cardiac repair process (18). The general feasibility of this approach was suggested by the observation that mice expressing the oncoprotein simian virus 40 T antigen (SV40-Tag) develop unilateral right atrial tumors (rhabdomyosarcomas) consisting of highly differentiated atrial cells (89, 90). Oncoproteins immortalize by an interaction with cell cycle proteins; therefore, these studies suggested that cardiomyocyte growth might be reactivated in adult cells through the manipulating the cell cycle (91, 92) or by alternative means to enhance the replicative potential of cardiomyocytes (93). This novel approach has begun to be tested. Expression of the E1A oncoprotein or the transcription factor E2F-1 in neonatal cardiomyocytes induced DNA synthesis and triggered apoptosis (91, 94). The cardiac restricted expression of cyclin D produced multinucleated cardiomyocytes in trangenic mice (92). We expect this approach to be actively developed in the next few years, with a caveat that this approach will require a tightly regulated system of gene expression because of concerns regarding neoplastic transitions in these altered cells.

INTRODUCING NEW CELLS INTO THE CARDIAC ENVIRONMENT

The introduction of new cells into myocardium is the best studied of the strategies for myocardial repair and is the focus for the remainder of the review. This strategy assumes that grafted cells demonstrate a normal response to physiological stimuli. Fundamental questions common to all cell sources are identification and survival of grafted cells, differentiation of implanted cells, host-cell interactions, and mechanical and electrical coupling of implanted cells. Although use of fetal cells in studies has proven important, it remains ethically controversial. Important issues that remain unanswered include the ideal source for cells (allogeneic or autologous) and the role of genetic enhancements of the grafted cells or recipient bed as a means of enhancing the survival of grafted cells or of engineering a more favorable response to hypertrophy or ischemia.

CARDIOMYOCYTE GRAFTING The possibility of transplanting cardiac muscle
cells grown in culture was first explored by Steinhelper et al (95) and Delcarpio et al (96). Atrial tumors were isolated from transgenic mouse tumors produced by atrial expression of SV40 large T antigen. The tumors were propagated as subcutaneous tumors in syngeneic animals to generate a cell line that has the characteristics of differentiated atrial cells, called AT-1 cells (95, 96). Grafts of these cells into the ventricle demonstrated retained mitotic activity and long-term survival AT-1 cells, without the formation of gap junctions with native myocardium (8). A cell line derived from AT-1 cells, called HL-1 (97), has been introduced into normal and infarcted pig myocardium. These cells formed stable grafts when grafted within the normal porcine myocardium, with formation of adherens junctions and gap junctions, but they failed to survive in a myocardial infarction model (98).

It was also demonstrated that embryonic cardiomyocytes could be grafted into murine and canine hearts (6, 7). Intercalated disk formation, gap junctions, and connexin-43 staining were observed at interfaces between
grafted cells and host myocardium, confirming stable incorporation of grafted cells into the myocardium. Similar close associations with intercalated disk formation were observed when human fetal cardiomyocytes were grafted into normal porcine myocardium (99), or when murine fetal cardiomyocytes were labeled with an adenoviral vector prior to transplantation (100).

When the grafting studies were extended to include models of myocardial injury, fetal human and rat cardiomyocytes formed stable grafts within the myocardial scar up to 65 days after transplantation for myocardial infarction (101). These studies demonstrated that the cardiac environment was hospitable for grafts across species and demonstrated an angiogenic response to the grafting process that may be related to autocrine substances released from grafted cells (98; see also 102). In coronary occlusion/reperfusion, grafting of fetal cardiomyocytes was associated with improved left ventricular function as assessed by

echocardiography (103). Similarly, grafts of fetal rat cardiomyocytes, administered 4 weeks after cryoinjury of the left ventricle, were associated with improved function, when assessed in the excised %%%heart%%%
, and with limited myocardial scar expansion (102, 104). Therefore, in the absence of mechanical or electrical coupling (as the grafted cells were encased in scar), the presence of cells exerted favorable effects on ventricular function and geometry. In contrast, Connold et al (105) identified gap junctions between grafted cells and damaged myocardium. Nevertheless, the contractile effects of cardiomyocytes, passive mechanical properties of the graft, or effects on angiogenesis may have contributed to the beneficial effect of cardiomyocyte transplants in myocardial infarction. An ethical objection to the use of fetal tissues may be addressed by the development of human embryonic stem cells and the genetic
selection of cardiomyocytes from these stem cells (see 9).

GRAFTING OF SKELETAL MYOBLASTS The use of skeletal muscle as a passive
graft to rebuild the %%%heart%%% dates from Leriche & Fontaine (106), who
used a passive graft of skeletal muscle to repair a cardiac defect. The modern experimental surgical procedure, dynamic cardiomyoplasty, provided evidence that autologous grafts of skeletal muscle grafts could be adapted to perform cardiac work and enhance cardiac function. In this experimental surgery, vascularized grafts of left latissimus dorsi muscle were wrapped around the epicardial surface of the %%%heart%%% in the orthotopic position
and rhythmically stimulated with a pacemaker to condition the muscle (24). This ability of skeletal muscle to transform into indefatigable muscle was based on the biochemical and physiological plasticity of skeletal muscle (reviewed in 107). Chronic electrical stimulation of fast-twitch skeletal muscle induces the expression of slow-twitch isoforms of contractile and sarcoplasmic reticulum proteins, including myosin heavy chain, calcium ATPase (SERCA2a), and the slow-twitch/cardiac protein %%%phospholamban%%%
(108-111). These proteins contribute to the slower contraction and relaxation rates of slow-twitch skeletal and cardiac muscle fibers. The plasticity of skeletal muscle in response to electrical depolarization, and the clinical experience with dynamic cardiomyoplasty, suggested that individual myoblasts might be converted to muscle fibers that are capable of performing cardiac work.

The initial experiments determined the fate of myogenic cells grafted into the hearts of syngeneic animals (3-5) or autologous satellite cells grafted into %%%heart%%% (1, 2, 112, 113). Myogenic cell lines were used because they had been extensively characterized, and they proliferate in culture as pure populations. Myogenic cells derived from rodents, such as L6 and BCH1, have been produced by %%%treatment%%% with chemical mutagens
and form tumors in vivo. The C2C12 mouse myogenic cell line, however, was generated by spontaneous immortalization of rodent muscle (114). Murine C2C12 myoblasts enter the resting phase of the cell cycle in response to lowered levels of serum and remain mitotically quiescent, thus recapitulating myogenic differentiation. Potential problems associated with the use of these cells include the potential for tumor formation (115) and genetic drift of the cell line.

Grafts of autologous cells minimize the risks of neoplasia and immune rejection associated with allogeneic or xenogeneic cells. However, immunomodulation to allow the survival of allogeneic or xenogeneic cells can be achieved using conventional immunosupressive agents (102) or strategies to induce donorspecific tolerance (116). Protocols for the growth and maintenance of autologous skeletal myoblasts isolated from adult muscle were established (117). These primary cultures can be expanded in large numbers up to 1017 cells per clone. However, they can contain 50[percent] nonmyogenic cells (118) and generally require adenoviral vectors to efficiently label (113, 119). In contrast, myogenic cell lines can be easily modified with plasmid DNA to contain a genetic marker or transgene (115, 120).

Transmural and arterial delivery of myoblasts Successful delivery and long-term survival of skeletal myoblast grafts in the myocardium have been achieved by intramural implantation (1-4) and arterial delivery (5, 113, 118). Both approaches might be adapted for use for myoblast transfer in patients. Implanting myoblasts into the wall of the %%%heart%%% is relatively simple: Cells are suspended in phosphate-buffered saline or medium and then directly injected into the ventricular wall using a small-gauge needle. Although scar formation is observed at the injection site in mice, in larger animals the needle path is often difficult to identify.

Arterial delivery was achieved with a transventricular injection in small rodents (5) or by selective coronary injection in larger rodents (113). Arterial delivery of skeletal myoblasts has several advantages over direct infiltration into the myocardium, notably an approach that parallels endovascular methods in clinical practice. It is likely that adult myoblasts (satellite cells) do not normally migrate into the bloodstream (121). However, arterial delivery of L6 skeletal myoblasts to rat skeletal muscle had been demonstrated, confirming the capacity of immortalized myoblasts to cross the endothelium into the muscle interstitium (122). Additionally, myogenic progenitor cells may be mobilized from bone marrow and traverse the circulation to reach injured muscle (see discussion of mesenchymal stem cells below) (12), and following the vascular delivery of endothelial cells and mesenchymal stem cells, engraftment of vascularized organs occurs (123, 124).

The fate of skeletal myoblasts following their introduction into the arterial circulation of the %%%heart%%% was predicted to be analogous to intraventricularly injected tumor cells. Murine melanoma cells arrest in the coronary capillaries and undergo lysis within 5 min (125, 126). In studies performed by Robinson et al (5), within seconds of injection into the ventricular cavity, genetically labeled C2C12 cells were distributed throughout the left and right coronaries, entrapped in the lumina of small capillaries. One week after injection, the cells were no longer found in the capillaries but appeared to be integrated into the myocardial interstitium; 72[percent] of the animals injected continued to show labeled cells for as long as 6 months (5). No histological evidence of myocardial thrombosis or infarction was observed, and electrocardiograms of sham-injected and myoblast-injected animals appeared similar.

Differentiation of implanted cells Skeletal muscle develops along an orderly pathway, with commitment of stem cells to the myogenic lineage (myoblasts), proliferation of myoblasts, and fusion to form myotubes. Following introduction in the %%%heart%%%, primary myoblasts (113, 118) and
myogenic cell lines (3, 5) parallel the normal developmental process for myoblasts, with cell cycle exit and myogenic differentiation (as assessed by proliferating cell nuclear antigen (PCNA) staining) (5), the expression of fast-twitch skeletal muscle isoforms of myosin heavy chain (3, 118), SERCA1 (5), and formation of myofibrils (3, 5, 118). SERCA1 expression was present for at least 6 months after implantation. These findings suggested that the cardiac environment was permissive for myogenic differentiation. Myogenic differentiation occurred when cross-species transplants were performed with immunodeficient recipients (SW Robinson, PD Kessler, unpublished data).

Alteration in the phenotype of implanted cells to a slow-twitch phenotype %%%Phospholamban%%% is expressed in cardiac cells and slow-twitch
skeletal muscle. The induction of %%%phospholamban%%% expression during electrical stimulation of skeletal muscle has been reported (110, 111). Robinson et al (5) identified myoblast-derived cells that coexpressed %%%phospholamban%%% and the fast-twitch marker, SERCA1. Murry et al (118)
also identified primary rat myotube cells that expressed a slow-twitch isoform of myosin heavy chain. The mechanism for the induction of slow-twitch gene expression in these grafted cells is unknown. In view of the induction of the slow-twitch phenotype in skeletal muscle grafts encased in scar, an aspect of the cardiac milieu altered the developmental program of the implanted cells, switching them to a slow-twitch phenotype rather than to a cardiac phenotype.

Electromechanical coupling of implanted cells Cardiac cells are electrically coupled to adjacent cells via specialized gap junctions, composed of hexamers of the protein connexin-43, that allow the exchange of
ions and small molecules between adjacent cells (127, 128). Gap junctions are found in virtually every cell type in mammals; adult skeletal muscle fibers are a notable exception. These junctions have been identified in developing avian and rodent muscle fibers and primary cultures of these cells (129-131), and connexin-43 has been identified in cultured L6 myoblasts prior to fusion (132). In addition, connexin-40 is expressed in neonatal fibers (133).

When skeletal myoblasts were introduced into normal murine %%%heart%%%
or cryoinjured rat %%%heart%%%, analysis of the graft-host myocardium junction failed to demonstrate evidence for mechanical or electrical coupling between skeletal and cardiac cells (3, 118). In unpublished studies, neither connexin-43 staining nor structures that resemble intercalated disks between host myocardium and intramural grafts of

genetically labeled C2C12 myoblasts were observed (SW Robinson, PD Kessler
unpublished information). Interestingly, Murry et al (118) described structures resembling adherens junctions and tight junctions within the grafts. The observed junctions may represent couplings between two adjacent
myoblast-derived structures, or between myoblast-derived structures and smooth muscle (10), fibroblasts (134), or perhaps putative intracardiac mesenchymal stem cells (see below) (135, 136). That junction formation was not consistently observed among myoblast-derived cells (3, 5) may be due to differences in species, in animal model, or between primary and immortalized cells. The electrical couplings observed by Murray et al (118) may be similar to the low-resistant junctions described during the fusion of myoblasts in vitro (130, 131).

Putative electrical coupling when C2C12 myoblasts are delivered via the arterial circulation That coupling between intramurally delivered skeletal myoblasts and host myocardium has not been observed when myoblasts
are infiltrated into the ventricular wall may be due to the formation of a scar tissue that effectively isolates grafted cells from host cells. Dense scar is described in cryoinjury and may isolate implanted cells from surrounding myocardium (1, 2, 118, 137). The intramural injection of myoblasts into uninjured rodent %%%heart%%% is accompanied by a transient
increase in cardiac lactate dehydrogenase (LDH) isoenzymes, consistent with myocardial injury (3).

When myoblasts were delivered via the arterial circulation, connexin-43 was immunolocalized to some sites of donor and host cell contact (5). Fine-structure analysis demonstrated electron-dense thickenings at cell-cell interfaces, consistent with spot desmosomal junctions. Surpringly, this observation is not novel. Terasaki et al (10) identified desmosomes and fascia adherens junctions between cardiomyocytes
and subendocardial smooth muscle cells in situ. We observed structures in several independent cell pairs that resembled intercalated disks, and observed a structure at the interface of the two different cell types, that appeared to be a gap junction (5). Taken together, these data suggest that components of an electrical coupling system might be present in some engrafted cells that survive 5-6 months. Confirmation of electrical coupling will require demonstration of the transfer of small tracer molecules between myoblast-derived cells and cardiomyocytes.

Functional effects of myoblast grafting More relevant to the problem of myocardial repair has been the experience with grafting primary cells into injured myocardium. Primary myoblasts have been grafted into the cryoinjured myocardium of dogs, rabbits, and rats (1, 2, 118, 137). This injury approximates a myocardial infarction, without subsequent aneurysm formation. Collectively, these studies clearly demonstrated the long-term survival and differentiation of implanted cells. Importantly, functional improvement in left ventricular function after myocardial injury was observed (118, 137).

In contrast to experience with myoblast grafting into skeletal muscle (138), there have been few estimates of the efficiency of myoblast grafting into %%%heart%%%. In fact, grafted cells frequently failed to survive in rabbit cryoinjury (137). Arterial injection of myoblasts was relatively inefficient (5). After an injection of 106 cells, about 50,000 would be expected to partition to the coronary circulation, which receives about 5[percent] of the cardiac output in mice (126). In fact, in our hands, only about 700 LacZ-positive cells were present in the %%%heart%%% 1 week after
injection (5). In contrast to these results, when Taylor and coworkers (113) performed selective coronary injections of myoblasts in rabbits, they were able to achieve high-efficiency delivery to the myocardium via the coronary circulation. The mechanism for the translocation of myoblasts is unknown, and it may be favorably affected by transient ischemia related to capillary plugging.

Unanswered questions There are many unanswered questions about this approach. Although some workers have suggested that an implanted cell undergoes transdifferentiation into a cell that has a cardiac phenotype (1), the existing evidence supports conversion of implanted muscle to a slow-twitch phenotype (5, 118). It may be advisable to manipulate implanted cells so they remain mononuclear to enhance the number of surviving cells (34), or perhaps a delay of myogenic differentiation may elicit a cardiac phenotype. It is unlikely that heterokaryons form between cardiac and skeletal muscle, and in fact they may not be advantageous (74). Although specialization of the multiple nuclei of the myotube is well understood (139, 140), it is unclear if similar specialization will develop for myotubes that differentiate within the cardiac environment.

MESENCHYMAL STEM CELLS (MARROW STROMAL CELLS) The bone marrow
contains, in addition to blood-forming progenitors, cells that have the properties of stem cells (reviewed in 141, 142). These cells are referred to as marrow stromal cells or mesenchymal stem cells (MSCs). It has been hypothesized that MSCs derived from the marrow of post-natal animals can serve as a continuing source of progenitor cells that give rise to mesodermal tissue, such as cartilage, bone, muscle, fat, and tendon (141-143). These adherent cells have been shown to be multipotential, and under appropriate culture conditions they differentiate into osteoblasts, adipocytes, chondroblasts, and skeletal muscle. MSCs are similar to the murine mesenchymal stem cell line, C3H10T1/2. Following %%%treatment%%%
with 5-azacytidine, C3H10T1/2 and MSCs are capable of differentiating into multiple lineages, including muscle, cartilage, and fat cells (144-146). C3H10T1/2 cells also show osteogenic, adipogenic, and chondrogenic differentiation upon exposure to BMP-2 and BMP-4 (147).

In contrast to the hematopoetic and endothelial stem cells, MSCs are derived from somatic mesoderm. There is no evidence for a common stem cell
that gives rise to hematopoetic and stromal progenitors (148). In vivo, MSCs can form cartilage or bone after implantation in ceramic cubes (141), or they can become incorporated into normal or dystrophic skeletal muscle fibers (12, 149). More homogenous populations of these cells have been prepared recently, and they have been explored as a vehicle for cell-based gene therapy and cellular repair (124, 149-151). Marrow-derived cell populations have an advantage as an autologous cell source, as they are easy to isolate and may be unaffected by systemic %%%disease%%%.

After systemic injection, MSCs can repopulate a number of organs (150). Following a systemic injection, MSCs were detected in lung, cartilage, and bone, but not %%%heart%%% (150). More recently, it has been
suggested that bone marrow stromal cells or another population of cells present in the marrow may participate in skeletal muscle regeneration (12, 149). In murine muscle regeneration, bone marrow-derived cells migrated to the site of muscle injury and were incorporated into muscle fibers (12). This supplemental repair program may be important in states that are characterized by impaired satellite cell function, such as aging or myopathy (see above).

Might MSC be present in extramedullary sites? There is evidence that MSCs or MSC-like cells may be present in %%%heart%%%. The cardiomyocyte
cell line, H9C2, isolated from cardiac fibroblasts demonstrates aspects of the cardiac and skeletal phenotype (152). Recently, cells were isolated from neonatal rats that had the potential to differentiate into several mesodermal phenotypes, including binucleate cardiomyocytes, and that behave
like MSCs (135). Also isolated were MSC-like cells from the skeletal muscle of neonatal rats (153) and embryonic chicken (136), and similar cells have been isolated from the atria and ventricles of chick %%%heart%%% (154). Moreover, a recent abstract reported that 5-azacytidine induced conversion of murine bone marrow stromal cells into cardiomyocyte-like cells (155). Clones were derived that formed a syncythium in vitro, which beat synchronously, and expressed cardiac markers, including NkX2.5 and GATA-4.
Further confirmation of these findings is eagerly awaited, but collectively these data and those of Warejcka et al (135) suggest an interesting possibility: An MSC or another stem cell, resident in bone marrow or %%%heart%%%, might be converted into a cardiomyocyte-like cell when placed
in the proper environmental context. This possibility has been stimulated by the notion that progenitor cells for nonhematopoetic tissues (endothelial or myogenic precursor cells) are present in bone marrow and participated in repair processes in the adult vertebrate (12, 156). Most interestingly, studies by Eisenberg et al (157-159) suggest that a pluripotent cell exists during early development that has the capacity to differentiate into endothelium, hematopoetic cells, or cardiomyocytes. We do not know if this cell population overlaps with the population of MSCs, although embryological considerations suggest they may not. We have begun to evaluate bone marrow-derived cells as a source for cells that might be adapted for cardiac repair. Toward these ends we have demonstrated the survival of MSCs when grafted into the %%%heart%%% (11; C Toma, P Gruber,
PD Kessler, BJ Byrne, M Pittenger, unpublished information), and we anticipate this may be a fruitful area of research in the future.

CLINICAL IMPLICATIONS

IMPLANTED CELLS AS A PLATFORM FOR PROTEIN DELIVERY

The utility of genetically modified C2C12 cells as a platform to deliver recombinant TGF-b1 has been demonstrated (4). Myoblasts are able to process
a variety of recombinant proteins with proper posttranslational modification of secretory proteins (160). Recombinant myoblast transfer to the %%%heart%%% might be useful for local expression of neurotrophic factors and angiogenic factors and may avoid the potentially harmful effects of systemic delivery of these proteins (160). Transcriptional regulation remains one of the greatest challenges when such a strategy is used. A potential advantage of placing extra cells in the implantation site is that fine control of the amount of gene expression may be achieved by selective elimination of some of the implanted cells using suicide genes engineered into the cell.

GENETIC ALTERATION OF CELLS AND ENVIRONMENT

The ability to genetically alter implanted cells or the environment may have profound effects on the results of cell transplantation. The inactivation of the interferon-g receptor in murine myoblasts by homologous recombination suggests the possibility of engineering myoblasts with a favorable profile for myocardial repair or gene transfer (161). Insights into the mechanism of translocation of cells across the capillary bed may allow us to engineer cells designed for enhanced cell transfer.

Methods of gene transfer that have been utilized to genetically modify myoblasts include plasmid DNA, retrovirus, adenovirus, and adeno-associated virus vectors (5, 118, 162, 163). Cells engineered to overexpress metaloproteinases might allow for enhanced myoblast egress from the circulation, or reduce fibroblast and matrix deposition, which may encase the grafted cells. Alternatively, immunomodulatory molecules, such as the CD 95 (Fas) ligand expressed on allogeneic cells, may allow for the long-term engraftment of genetically dissimilar cells (164).

METHODS TO DELIVER CELLS IN THE CLINICAL SETTING

In order to enhance cellular graft survival and improve the region of distribution in the myocardium, several technical challenges will have to be met. Given the ability to isolate sufficient quantities of syngeneic donor cells, the first obstacle to successful tissue repair with myogenic cells will be the method of delivery of the cells. Placement of the cells in the myocardium may be accomplished by a direct epicardial injection into pre-identified zones of ischemic risk or cardiomyocyte loss. Presumably, such a procedure would be done at the time of another cardiac intervention, such as revascularization surgery or implantation of a ventricular assist device. An alternative approach to epicardial delivery is via thoracoscopy. Over the past few years, minimally invasive surgery has transformed the approach to a number of surgical procedures. Surgical expertise and interest in minimally invasive surgery has increased with the development of new protocols and techniques to perform a variety of such procedures, including coronary artery bypass surgery and valve-replacement surgery (165). These new methods allow the surgeon to work on the %%%heart%%% through a small incision between the ribs. The further development of endoscopic techniques will allow for the introduction of cells into the %%%heart%%% without a median sternotomy. Alternatively, endovascular techniques, using modification of the transmyocardial revascularization technique, might be utilized to deliver cells to the %%%heart%%%. Steerable
catheters may be utilized to enter the endocardium to place endocardial plugs ("myocardial sodding"). If placed closely together, and allowing for a small degree of cellular proliferation, these plugs might result in a mechanical benefit for the %%%heart%%% tissue. Finally, direct arterial delivery of cells (5, 113) via the coronary circulation might be attempted. Once the cells are implanted into the interstitial space, strategies to enhance transdifferentiation of implanted cells may be necessary, whereas this approach will be unnecessary if cardiomyocyte-like cells are implanted. One of the strongest signals for transdifferentiation may be the mechanical or electrical environment of the working %%%heart%%%.

Phase I clinical trials of cell implantation in the damaged %%%heart%%% could easily be achieved in patients undergoing placement of left ventricular assist devices or ventricular reduction surgeries (22, 23). Patients undergoing left ventricular assist device placement have intractable %%%heart%%% %%%failure%%% and are candidates for cardiac transplantation. Therefore, the implanted cells can be reexamined when the transplantation surgery is performed and the explanted %%%heart%%% is available for detailed histologic examination. This ambitious program for clinical development will depend on further demonstration of the efficacy and safety of grafting in preclinical models.

CONCLUSION

This review chronicles the current state of the art for the grafting of mesodermally derived cells. Collectively, the findings suggest that myoblasts can form stable grafts in the %%%heart%%% and that signals originating in this environment may alter the phenotype of skeletal muscle-derived cells. Further studies are needed to characterize the interactions between implanted cells and native myocardium, and to develop methods to enhance this interaction. The success of this approach will require the integration of a number of disciplines: molecular biology, bioengineering, matrix and tissue engineering, gene therapy, medicine, and surgery. Promising areas for research in the next millenium include identification of factors that can maximize grafted cell survival and strategies that might convert cells into cardiomyocytes.

Added material

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4/7/65 (Item 2 from file: 98)
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04014395 H.W. WILSON RECORD NUMBER: BGSI99014395 (THIS IS THE FULLTEXT)
Excitation-contraction coupling in gastrointestinal and other smooth muscles.
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ABSTRACT: The main contributors to increases in {Ca2+}i and tension are the entry of Ca2+ through voltage-dependent channels opened by depolarization or during action potential (AP) or slow-wave discharge, and Ca2+ release from store sites in the cell by the action of IP3 or by Ca2+-induced Ca2+-release (CICR). The entry of Ca2+ during an AP triggers CICR from up to 20 or more subplasmalemmal store sites (seen as hot spots, using fluorescent indicators); Ca2+ waves then spread from these hot spots, which results in a rise in {Ca2+}i throughout the cell. Spontaneous transient releases of store Ca2+, previously detected as spontaneous transient outward currents (STOCs), are seen as sparks when fluorescent indicators are used. Sparks occur at certain preferred locations--frequent discharge sites (FDSs)--and these and hot spots may represent aggregations of sarcoplasmic reticulum scattered throughout the cytoplasm. Activation of receptors for excitatory signal molecules generally depolarizes the cell while it increases the production of IP3 (causing calcium store release) and diacylglycerols (which activate protein kinases). Activation of receptors for inhibitory signal molecules increases the activity of protein kinases through increases in cAMP or cGMP and often hyperpolarizes the cell. Other receptors link to tyrosine kinases, which trigger signal cascades interacting with trimeric G-protein systems. With permission, from the Annual Review of Physiology, Volume 61, 1999, by Annual Reviews Inc. (http://www.annurev.org).

TEXT:

KEY WORDS: ultrastructure, ion channels, calcium events, signal transduction, sarcoplasmic reticulum

INTRODUCTION

Excitation in its original sense as applied to nerve and skeletal muscle meant the discharge of an action potential. In smooth muscles (SMs) contraction--or, indeed, relaxation of existing tone--may occur with or without a change in potential across the cell membrance (plasmalemma), although under physiological conditions it seems likely that changes in membrane potential normally accompany changes in tension. In SMs, including
those of the gastrointestinal tract, the electrical change triggering contraction is an action potential or some form of slower potential change (or which the "slow wave" is one example); the initiation of contraction by changes in the membrane potential has been termed electromechanical coupling (195). The change in membrane potential generally reflects changes in the conductance of the plasmalemma which, if not myogenic, are caused by activation of receptors by signal molecules or by stretch. Whether an action potential and/or a slow wave triggers contraction, it is likely that it is the entry of calcium through voltage-dependent channels which initiates the contractile process, although it is possible that sometimes depolarization itself plays a part. Because calcium is strongly buffered in the SM cell (buffering ratio, 30-227) (10, 63, 99, 100) the amount of entering calcium may be insufficient to raise the ionized calcium concentration, Ca2+ i, throughout the cytoplasm to the required level for contraction so that in many cases calcium-induced calcium release (CICR) is necessary. Conversely, relaxation of existing tension or tone is associated with hyperpolarization; this may inhibit existing action potential discharge or simply reduce the probability of voltage-dependent calcium channels being in the open state, both of which reduce voltage-dependent calcium entry.

However, a wider definition of excitation-contraction coupling has been suggested for SMs which includes, besides electronmechanical coupling, stimuli causing contraction which are not associated with electrical change in the membrane. Such mechanisms have been termed pharmacomechanical coupling (196, 197); this process involves activation of receptors which often increase Ca2+ i by releasing calcium from intracellular stores. Pharmaco-mechanical coupling generally involves the phospholipase C (PLC)/inositol-1,4,5-trisphosphate (IP3)/diacylglycerol (DAG) system and often a number of other mechanisms by which SM tension can be modulated or
even initiated through GTP-binding proteins (G proteins), phosphorylation and dephosphorylation reactions, and possibly others. Since pharmacomechanical coupling does not by definition involve an electrical event in the membrane, it might be argued that it does not strictly fall within the definition of excitation, although it has been deemed to do so in SM by custom and use. There are now many examples of synergism or interaction between pharmacomechanical and electromechanical mechanisms.

As in other muscles, calcium is believed to be the crucial signal for tension generation or shortening of the SM cell. However, important differences exist between SM and striated muscles; cardiac and skeletal muscle owe their striped appearance under the light microscope to the regular alternating arrangement of actin, myosin, and other contractile proteins, which gives rise to optically anisotropic bands. Other features of their ultrastructure reflect this repeating pattern of the contractile proteins: Calcium release, calcium sparks, and the arrangement of the calcium sotres are also organized on the same repeating, sarcomeric pattern (45, 184). The ultrastructure of SMs is very different from that of striated muscles, and it should not therefore come as any surprise that the control of the contraction process is also very different; actin, myosin, and associated contractile proteins show no regular repeat or sarcomeric pattern; the sarcoplasmic (endoplasmic) reticulum (SR), which is believed to be the major site of calcium stores, also shows no regular periodic arrangement but is scattered in the cytoplasm. Also, myosin-actin interaction in SMs involves a calcium-calmodulin-controlled phosphorylation of the myosin light chain, quite unlike the troponin-regulated system of striated muscles. In addition, it is believed that there is some thin-filament regulation of contraction through the phosphorylation of two proteins, caldesmon and calponin, which reduces their inhibitory influence on actin-myosin interaction (5, 44; but see 156). Although SM generally contracts more slowly than skeletal muscle, it can exhibit shortening to 25[percent] of its resting length (56) and, despite these differences from striated muscles, at optimum length it generates comparable force per cross-sectional area to striated muscle but has one-third of its myosin content; it does not show fatigue (41) and maintains tension at a much lower energy cost (167).

ULTRASTRUCTURE

A knowledge of the arrangement of the components of the contractile system
and the mechanisms for the local control of calcium movements within the

cell are essential for an understanding of the process of excitation-contraction coupling in SMs. While there are quantitative variations in SM structure, and occasionally special features, the basic arrangement of the contractile proteins and other intracellular organelles as seen in fixed specimens with the electron microscope is similar in all mammalian SMs, as has been known for more than 20 years (8, 40, 58, 60). The fusiform SM cell in its relaxed state is generally less than 5 mm wide transverse sections of guinea pig taenia caeci cells in the fully relaxed state have an average area of about 10 mm2, increasing about fivefold under conditions of extreme shortening (56) , and are up to 500 mm long, although in some situations, such as small blood vessels, they are much shorter, 20-50 mm (59). Thick myosin filaments 2.2 mm long are orientated roughly parallel to the long axis; the thinner and more numerous about 10-12 times (range, 5 to 27) (41, 58) actin filaments run parallel to the myosin filaments. Recent measurements indicate that they are 1.35 mm long (41). They are inserted either into dense bodies scattered within the cytoplasm or into dense bands (attachment plaques) inserted on the internal surface of the plasmalemma. Dense bodies and bands contain a-actinin and have been compared to the Z-line in striated muscles; they differ in that dense bands, but not bodies, contain vinculin (192). Tension or shortening of the contractile filaments pulls on the dense bands, causing invagination of the surface membrane at these points.

Between the sites of attachment of the dense bands are rows of flask-like caveolae intracellulares of uncertain function; two proteins, dystrophin and caveolin, are associated with the region containing these caveolae (158). Caveolin interacts with heterotrimeric G proteins, and three caveolin isomers encoded by separate genes have been identified (198, 206). Intramembranous particles have been described as surrounding the necks of caveolae (57). Especially in phasic SMs, the caveolae commonly have associated with them (within 100 nm or so of the surface plasmalemma) a network of SR tubes and fenestrated sacs in which calcium is believed to be stored. The SR contains the calcium storage proteins calsequestrin and calreticulin (136, 223) and %%%phospholamban%%%, a regulatory protein of the SR calcium pump (SERCA) (52, 173); SERCA can also be regulated in some
SMs by direct phosphorylation by calmodulin-dependent kinase (72). The gap between the base of the caveolae and the SR membrane is shown by electron microscopy of fixed tissues to be frequently less than 20 nm, and a similar gap may separate the plasmalemma from the SR membrane in regions where caveolae are absent (40, 55); sometimes small feet are seen bridging this gap (40). Another SR, deeper within the cytoplasm, is often found extending from or associated with the Golgi apparatus or nucleus or arranged in collections of lamellae within the cytoplasm. Connections between superficial (subplasmalemmal) and deep (central) SR do occur (40, 55, 157). It is claimed that phasic SMs (e.g. vas deferens) have mainly subplasmalemmal SR, whereas tonic SMs (e.g. aorta) have small but well-developed deep SR (40, 123, 157). Mitochondria, also implicated in calcium uptake and storage (42, 70), are scattered within the cytoplasm.

Present evidence favors the idea that there are two distinguishable regions of the SM plasmalemma, one serving a force-transmission function and the other representing the site of ion exchange through channel and pump activities (158); the latter is associated with the rows of caveolae intracellulares. These two regions are arranged as roughly alternating longitudinal bands on the SM cell surface (58). When labeled antibodies were used, vinculin, a component of the dense bands to which the contractile proteins are anchored, was found not to be colocalized with either the Na/Ca exchanger or the Na/K pump. However, these were colocalized with each other and the Na/Ca exchanger also colocalized with calsequestrin (141), a calcium-binding protein found particularly in the subplasmalemmal SR (157, 215). It had been suggested on the basis of calcium oxalate precipitation experiments that the caveolae are the sites of calcium extrusion (170), and more recently immunocytochemical experiments have supported this (53). A body of indirect evidence supports the idea that calcium released from the plasmalemmal side of the superficial SR into the narrow subplasmalemmal space between it and the plasmalemma may be extruded by the plasmalemma Na/Ca exchanger rather than
escaping into the general cytoplasm (116, 214). It seems possible that the caveola-rich regions between dense bands represent regions of the SM plasmalemma where ion channels and pumps are found; calcium entering through voltage-dependent channels may trigger CICR from the SR in these regions since colocalization of plasmalemmal calcium channels and SR ryanodine receptors (RyRs) in bladder SMs has been demonstrated by using fluorescent antibodies (33). Caveola-rich regions may also be the location of receptors linked to ion channels and to the PLC/IP3 system, since the superficial SR has also been shown by immunogold staining to be rich in IP3 receptors (54, 157, 215).

Besides actin and myosin filaments, there are also intermediate filaments containing desmin (skeletin; reported to be replaced by vimentin in vascular smooth muscle) (123), which are considered to be part of the cytoskeletal system. These insert into both dense bodies and bands. In addition, there are a number of other proteins that can be extracted from the muscle and that are considered to be part of the cytoskeletal system, although some of these have been implicated in the control of the contractile process; these include a-actinin, filamin, gelsolin, laminin, vinculin, and vimentin (200); filamin and gelsolin have been suggested to inhibit the action of caldesmon on actin filaments and thus to facilitate contraction (39, 74). Suggestions that distinct cytoskeletal and contractile protein domains exist were not borne out by studies of actin isoform distribution (41).

PLASMALEMMAL ION CHANNELS

Gastrointestinal SM generally shows slow waves of potential change; sometimes it is a matter of arbitrary definition whether a transient potential change should be regarded as an action potential or a slow wave. The form of potential changes recorded from some SMs can be variable, and graded transitions between overt action potentials and slow waves are frequent; in other cases, the form of potential change can be quite characteristic for a particular SM. The ion channel events underlying slow-wave changes are poorly understood. The action potential in mammalian SMs of many types involves mainly an influx of calcium through voltage-dependent calcium channels, but in some SMs, sodium channels make a
substantial contribution to the upstroke of the action potential. Although during the repolarization phase of the action potential there is partial inactivation and deactivation of the calcium channels, this phase is due mainly to the opening of a variety of potassium channels. These include delayed-rectifier (Kv) and calcium-activated large conductance (BKCa) channels. Other potassium channels also contribute to the form of the electrical activity in some SMs or under some conditions: These include small conductance calcium-activated (SKCa), inward-rectifier (KIR), and A-type (KA) potassium channels, potassium channels sensitive to the internal concentrations of ATP and nucleoside diphosphates (KATP), and an M-current (KM) in toad gastric muscle. A cation channel activated by hyperpolarization (If) causes inward rectification. Chloride channels have also been described (202); some of these are calcium activated (ClCa) (117). Following their discovery in other tissues (see e.g. 9) volume-activated chloride channels have recently been found in vascular smooth muscle (151, 242) and are likely to be of widespread occurrence.

Activation of receptors may open potassium (BKCa, SKCa, or KATP) or chloride channels (201) to alter excitability and tension. Receptors for excitatory substances often open cationic channels, close potassium channels (KM), or, by raising Ca2+ i, open ClCa channels; all cause depolarization. BKCa channels may also be opened, and this presumably acts to limit the depolarization where it occurs. Cationic channels opened by stretch, Ca2+ i, or caffeine and potassium channels opened by fatty acids have also been described (for reviews, see 21, 130).

The properties of ion channels in the plasmalemma largely determine the form of electrical activity shown by smooth muscles; most gastrointestinal muscles discharge action potentials or slow waves, and these reflect the activities of their plasmalemmal ion channels modified by cell-cell interactions and by the presence of membrane pumps, which are electrogenic. At present, detailed reconstructions of the form of membrane electrical activity in SMs are few (115). There is information on the types of channels present in SMs, but there are many SMs, and probably much remains to be discovered.

CALCIUM CHANNELS

The voltage-dependent calcium current in many SMs is not a homogeneous current, since components with differing properties can be distinguished by holding at different potentials; thus, low-threshold and a high-threshold currents are sometimes distinguished. These are sometimes equated with transient, T, and longer-lasting, L, currents as described for other cell types, which are rapidly and more slowly inactivating and show different sensitivities to blockers such as Ni2+ and dihydropyridines, respectively (see e.g. 2, 15). The channel events underlying the calcium current(s) have usually been investigated by using high concentrations of Ba2+ on the outside of cell-attached patches; under these conditions, single-channel currents corresponding to conductances around 5-10 pS and 20-30 pS have often been described (175, 217, 240), with the occasional presence of

channels of an intermediate (about 15-pS) conductance (51). Exceptional single-channel recordings have been made with as little as 0.5 mM calcium in the recording pipette, and the conductance of the 20-30-pS channel in the physiological range, between 1 and 2 mM calcium, was 5-8 pS (103). The largest-conductance channels are believed to be responsible for the L-type current and the smallest for the T-type current, and it has sometimes been possible to demonstrate this by reconstruction of the global currents from single-channel events by repeated voltage steps. The role of channels with the intermediate conductance is obscure. Although differences of these types can be discerned in some visceral SMs (237), it is seldom possible to unambiguously equate the activity of the small- and large-conductance channels with the T- and L-type whole-cell currents (217, 240), and variations in pharmacological properties of the currents are also found (2). It seems possible that modulation of calcium channel properties can occur as a result of metabolic processes in the cell; added to this, there are different sensitivities to blocking agents for reasons which are as yet obscure but are probably related to the expression of modulating systems in some SMs and not others; in addition, differences in channel structure possibly caused by combinations of different channel subunits (175) and alternative splicing of the genes (228) are involved.

Heterogeneity of the calcium current is by no means the rule, and in several gastrointestinal SMs the calcium current appears homogeneous in that different components cannot be distinguished by the use of different holding potentials (4, 185, 241). The calcium current has been suggested to play an important role in slow-wave generation in canine colonic SM: A nifedipine-resistant component has been implicated in the initiation of slow waves, and a second, sustained, nifedipine-sensitive component of the same current is believed to be responsible for calcium entry into the cell during the plateau (219, 220, 226). The ionic mechanisms underlying the electrical rhythms of gastrointestinal SMs will be considered elsewhere in this volume (see chapters by G Farrugia and by K Sanders & B Horowitz, this volume). Although a number of ion channel types have been identified in gastrointestinal SMs, which exhibit slow-wave and action potential discharge, the exact contributions of these (and other) channels to the components of the slow wave and to the bursts of action potentials that slow waves sometimes exhibit are not known (179); in multicellular preparations, there is also the unquantified role of groups of cells with differing properties, such as the interstitial cells of Cajal (see e.g. 86, 209).

Receptor activation can frequently modulate the voltage-dependent calcium current in many SM cell types via a G-protein mechanism and/or phosphorylation. The G protein involved in guinea pig ileum has been described as pertussis toxin sensitive by some (171) and insensitive by others (212). In canine and human jejunum, motilin increased the calcium current (49); introducing cholera toxin or GTPgS into the cell via the pipette during single-cell recording potentiated the calcium current, which was not inhibited by pertussis toxin, suggesting the involvement of an a-protein subunit (as) (47). Potentiation of the calcium current in canine colon involved a cAMP-dependent mechanism, suggesting that the effects of cholera toxin and GTPgS may occur via adenylyl cyclase stimulation (106).

POTASSIUM CHANNELS

Some potassium channels are open at the resting membrane potential; these include the inward rectifier (152) and noninactivating (46) channels. In gastrointestinal SMs, a number of potassium currents can be activated by changes in potential; these include an A-current (218), calcium-activated current (3, 30, 37, 50, 222, 236, 245), and more than one type of delayed-rectifier current (29, 75, 140, 163).

Large-conductance calcium-activated potassium channels (BKCa) seem almost ubiquitously distributed in SM cells. They are characterized by a conductance of about 120 pS in quasi-physiological potassium gradients and about 250 pS in symmetrical high-potassium solutions. They are blocked by charybdotoxin and iberiotoxin in low concentrations and by tetraethylammonium (IC50, about 0.5 mM; higher concentrations will nonspecifically block other potassium channels). The synergism exerted by the combination of depolarization and a rise in Ca^{2+} i on their opening probability (14) would seem to make them ideally suited to open and repolarize the membrane following the opening of calcium channels at the upstroke of the action potential. They have been suggested to terminate the slow wave in SMs of the canine colon (32).

BKCa channels also open in response to an increase in Ca^{2+} i close to the plasmalemma as a result of a spontaneous transient release of calcium from stores in the cell. The resulting simultaneous opening of up to 100 BKCa channels is seen as a spontaneous transient outward current (STOC) in voltage-clamped cells held at potentials positive to Ek (12). The opening of BKCa channels can play an important role in the responses to a number of inhibitory hormones and transmitters that cause their open probability to increase, producing hyperpolarization (see below).

Following the isolation from bovine tracheal SM (65) of BKCa and cloning of its b-subunit (104), the channel has been cloned from canine colonic SM (222). Studies have also been done on two cloned contributors to the delayed-rectifier current, Kv1.2 (75) and Kv1.5 (163).

OTHER ION CHANNELS

Sodium channels have been found in several gastrointestinal and other SMs. They carry a voltage-dependent inward current that is transient and generally lasts less than 10 ms; the major inward current in cells showing sodium currents is carried by calcium and is much longer-lasting. The sodium currents show different sensitivities to tetrodotoxin, with IC50 as follows: rat ileum, 4.5 nM (193); rat colon, 130 nM; human colon, 14 nM (235); rat fundus, 870 nM; guinea pig ureter, 11 nM (146); and human myometrium, <100 nM (243). Differences in channel activation and inactivation ranges were also noticed, reinforcing the idea that voltage-dependent sodium channels of SM are a heterogeneous group.

Channels activated, and some inactivated, by stretch of the membrane have been reported. Stretch has been applied mostly by negative pressure to the pipette during whole-cell tight-seal recording, although sometimes single cells have been stretched between micropipettes (230, 231). Usually the channels activated allow cations to pass, and their opening is facilitated by hyperpolarization (229). Sometimes hyperpolarization-activated channels open more readily in stretched cells (80). Stretch has also been described to increase the current through voltage-dependent calcium channels (238). Stretch also activates a potassium channel, possibly via the release of fatty acids (161). Some cation channels are inactivated by stretching (81).

SIGNAL TRANSDUCTION MECHANISMS INVOLVING ION CHANNELS

Many receptors found on SMs of the gastrointestinal tract exert their effects on the cell through heterotrimeric G-proteins. These in turn modulate the activity of enzymes (such as PLC, and protein kinases) and ion channels. Some, such as the P2X-receptor (a purinoceptor), combine a ligand-binding site and an ion channel (159). Many receptors for growth factors have tyrosine kinase activity, and some have been implicated in regulation of Ca^{2+} i (76, 178). Receptors can be divided conveniently into those binding signal molecules that cause contraction (excitatory receptors) and those binding signal molecules that cause relaxation (inhibitory receptors). The actions of signal molecules on ion channels in SM have been recently reviewed (11, 31).

EXCITATORY RECEPTORS

These are commonly associated with G proteins, which link the activated receptors to intracellular effector mechanisms. Many types of excitatory receptor are linked through Gq, G11, G14, or G16 to PLC-b, which, from phosphatidylinositol-1,4-bisphosphate, generates DAG and IP3. IP3 acts on receptors on the SR and possibly elsewhere to release calcium; this causes a rise in Ca^{2+}i, which has secondary effects on other, calcium-activated or -modulated, channels, i.e. potassium, chloride, and sometimes cation channels. Increased opening probability of the latter two causes depolarization, which allows more calcium to enter through voltage-dependent calcium channels, often because of increased action potential discharge (31). DAG stimulates the activity of protein kinase C (PKC), which in turn phosphorylates a number of proteins involved in signal transduction and contraction (85, 155, 224) and modulates the activity of some types of channel (77, 137, 216). Changes in the membrane potential can apparently affect the activity of PLC-b and the rate of IP3 production (62, 97), as first shown by Best & Bolton (16).

The isoform PLC-g is linked to receptors for growth factors which have intrinsic tyrosine kinase activity; activation of some G-protein-coupled receptors has been reported to cause phosphorylation of PLC-g in vascular SM (174). A rise in Ca^{2+} i stimulates PLA2 (145) or PLD (190), generating arachidonic acid or DAG (via phosphatidic acid), respectively; in addition to an effect of Ca^{2+} i, PLA2 activity (145) and PLD activity (190) can be regulated by several other pathways. Arachidonic acid, besides being a precursor for prostaglandins and related eicosanoids, has actions of its own on channel function (149, 162, 186), on tyrosine kinase activity (see e.g. 26), and on myosin phosphorylation (195). Phosphatidic and arachidonic

acids can activate PLC-g (174). In recent years a large number of small GTPases have been identified that are involved in cell signaling through downstream kinase cascades. Interactions between these signaling systems and trimeric G-protein systems are now being described (see e.g. 20).

A common effect of the activation of G-protein-linked excitatory receptors is the opening of cation channels. The most extensively studied cation channel in SM is found in the longitudinal muscle of the rabbit and guinea pig ileum (13, 93, 248). This current has an unusual current-voltage relationship: from its reversal potential at 0 m V to about -50 mV, the current increases in proportion to the increase in the electromotive force, but as negativity is further increased, the current progressively declines. Cation currents with similar current-voltage relationships have been found in canine gastric corpus (187), pylorus (221), and colonic muscle (120). In guinea pig ileum, the opening of the cation channels is gated by receptor activation via a pertussis toxin-sensitive G-protein link (94, 108), but opening probability is strongly increased by an increase in Ca2+ i (93). In rat ileum and canine gastric fundus, the cation current may be gated by a rise in Ca2+ i concentration (96, 187). Single-channel conductance in canine colon SM was 30 pS (221). Submaximal activation of muscarinic receptors in guinea pig ileum results in oscillations of the cation current as a result of synchronous oscillations of Ca2+ i brought about by what appears to be alternating unloading and loading of calcium stores through the action of IP3 (107, 249).

Activation of other receptors such as histamine may elicit a cationic current (108). Caffeine has been described to open a cationic channel directly (73). In many vascular muscles, cation channels are commonly opened by activation of excitatory receptors (6). Sometimes cation channels themselves allow significant amounts of calcium to enter: ATP opens cation channels, admitting calcium in bladder SM (183).

The release of calcium from stores within the cell produced when the PLC/IP3 system is stimulated has secondary effects on calcium-activated plasmalemma ion channels. The opening of calcium-activated cation channels has already been mentioned. In some gastrointestinal muscles, the rise in Ca2+ i also causes the opening of calcium-activated chloride (96, 225) and calcium-activated potassium (129, 188, 225) channels. Regulation of ion channels in SM by calcium has recently been reviewed (31).

A number of other effects on SM ion channels have been described. An A-type potassium current in colon and other SMs was blocked by arachidonic acid (149). Inhibition of an M-type potassium current due to activation of excitatory receptors caused depolarization, an effect mediated by DAG and so far described only for toad gastric SM (36). Mammalian gastrointestinal SM potassium currents have also been described as being inhibited by excitatory receptor activation (114); in tracheal and colonic SM, BKCa channels are inhibited through a pertussis toxin-sensitive G protein (38, 110, 111). In bladder and esophagus SM, an ATP-sensitive potassium current is inhibited (24, 77).

INHIBITORY RECEPTORS

Inhibitory receptors (which cause relaxation or reduction in tension generation) are described as working largely through cAMP and cGMP kinases,
which in turn phosphorylate channels, enzymes, or membrane pumps. These actions reduce Ca2+ i by reducing calcium entry (through opening potassium channels and hyperpolarization) and by increasing calcium sequestration in stores and calcium extrusion from the cell (139, 173), possibly by increasing sodium-calcium exchange (142). In addition, effects on the relationship between tension generation and Ca2+ i are likely (194; reviewed in 109). The actions of nitric oxide (147) and carbon monoxide (48, 210) were believed to be mediated via activation of guanylate cyclase to increase the cGMP concentration (84). Three types of potassium channels in canine colon, one of which was BKCa, were opened by nitric oxide, partially through an increase in the cGMP concentration (105). Some inhibitory receptors, such as those activated by calcitonin gene-related peptide or b-adrenoceptor agonists, presumably accelerate the phosphorylation of the KATP (172, 244), BKCa (126), and delayed rectifier channels (1) by PKA through an increase in cAMP concentrations. In vascular muscle, increased opening of BKCa channels may be mediated by both cGMP phosphorylation (176, 207) and G-protein mechanisms (121); PKC activation causes inhibition (137). In tracheal SM, Gs protein mediated cAMP-dependent
phosphorylation of BKCa channels and an increase in opening probability occur in response to b-adrenoceptor activation (112, 177). In toad gastric muscle, b-receptor activation gates an M-type current inhibited by excitatory muscarinic receptor activation (189).

CALCIUM-INTRACELLULAR EVENTS

ELEMENTARY CALCIUM RELEASE EVENTS

Brief spontaneous transient increases in Ca2+ i as a result of release from stores were first detected in muscle cells by the opening of calcium-activated potassium channels, which gave rise to STOCs in voltage-clamped SM cells (12, 160). Spontaneous transient increases in Ca2+ i were later detected in cardiac (34) and skeletal (211) muscle by monitoring the fluorescence of the calcium indicator dye, fluo-3, introduced into the cell. The spontaneous localized transient increase in light emission from the fluorescent calcium indicator fluo-3 has been termed a calcium spark (34). In enzymatically dispersed SM cells from the longitudinal layer of the small intestine, the rise time of the spark is about 40 ms and sparks decay to half their maximum size within about 55 ms;
thus, the total event lasts about 200 ms at room temperature. Their width at half-maximum amplitude was about 2 mm, and the increase in resting fluorescence was 1.75-fold (69). In vascular SM cells, the rise time was about 20 ms and the peak increase in resting fluorescence was 3-fold, which decayed to half-maximum size in about 25-50 ms (7, 138, 150). However, in intestinal SM cells, spontaneous calcium events shorter and smaller than sparks were observed, casting doubt on the notion that the spark is the elementary calcium event (69).

STOCs in voltage-clamped single SM cells represent the opening of a few to a hundred calcium-activated large-conductance potassium channels (BKCa channels) (12). STOCs are believed to represent periodic discharges of calcium from the calcium stores within the cell; the stores are generally superficially situated, but in any case the cells in the relaxed state are seldom more than 5 mm wide, so that sparks, because they are around 2 mm wide at half-maximum size, will be sufficiently close to the membrane to raise the free-calcium concentration above the threshold for the opening of substantial numbers of BKCa channels (138, 150). The evidence that STOCs arise in this way has been recently reviewed (23). STOCs can be up to 1 nA in size, which represents the opening of perhaps as many as 100 BKCa channels simultaneously, and they last less than 100 ms at half-maximum size (12, 23, 160). Recently, we have observed in small mesenteric artery cells spontaneous transient inward currents (STICs) due to ClCa channel opening, which were related to sparks (TB Bolton & DV Gordienko, unpublished data).

The frequency of STOCs is strongly increased by depolarizing the cell (160), and it has been argued that they represent a response to overload of the calcium stores (12, 23), although there may also be a contribution from an increased sensitivity of the BKCa channels to internal ionized calcium brought about by the depolarization (14). In cardiac muscle, the frequency of sparks increased as the calcium loading of the SR was increased (34).

CALCIUM-INDUCED CALCIUM RELEASE

CICR involves a process whereby a rise in Ca2+ i triggers further calcium release from SR stores; this may happen when calcium enters the cell through voltage-dependent channels or when IP3 releases stored calcium, and
it is probably important for the propagation of intracellular calcium waves. It has been suggested that Ca2+ i must exceed 1 mM for CICR to occur (87); the relationship of RyRs to the source of the calcium flux will be crucial in achieving this threshold concentration. cADP-ribose may play a role in CICR (102). In single isolated enzyme-%%%treated%%% SM cells, CICR may be impaired compared to its action on the intact tissue. Depolarization of small intestine SM cells under voltage clamp evoked an inward followed by a transient outward current; the latter was abolished by acetylcholine or by caffeine, which deplete store calcium, suggesting that calcium entering through voltage-dependent channels releases stored calcium, which acts to open BKCa channels, transiently contributing to the outward current (12, 246, 247). CICR has also been described in bladder SM (61). The existence of CICR in portal vein SM cells has been denied (99), despite the findings in an earlier report (71). Evidence for limited CICR in coronary artery SM cells was found (63). Caffeine and acetylcholine also abolish STOCs, implying that sparks in SM arise by calcium release from the same store as that acted upon by entering calcium (12). In a careful study of calcium waves in cultured SM cells, Blatter & Wier (19) found that caffeine %%%treatment%%% abolished propagation of the wave and concluded
that CICR was crucial for this process.

CALCIUM WAVES

A calcium wave may be defined as a transient rise in intracellular Ca2+ i which propagates within the cell. The velocity of propagation of calcium

waves has been described to be in the range 10-50 mms-1 (19, 90, 127, 153, 233), although recently higher values, up to 260 mms-1, have been obtained (69); in these studies, the contribution of plasmalemmal electrical events was uncertain because the membrane potential was not controlled by voltage clamp. Since SM cells are often electrically excitable, as action potentials or slow waves propagate over the plasmalemma, they will give rise to propagating calcium waves within the cell as a result of calcium entering through voltage-dependent calcium channels and triggering CICR from the subplasmalemmal SR. Action potentials propagate at about 5 cms-1 (113), and slow waves propagate at about 1/10 of this velocity (180, 205). The much greater velocity of plasmalemma electrical events in SMs compared
with intracellular calcium waves raises the question of the physiological importance of intracellular propagation of calcium waves in these long narrow cells.

In an SM tissue where action potential propagation occurs at 5 cms-1, all parts of a single cell longitudinally orientated within the tissue will be excited on average within 10 ms even if the cell is 500 mm long. There will follow a phase of calcium entry into the depolarized cell, which will last some tens of milliseconds; during this phase, CICR will occur from superficial stores beneath the plasmalemma (91, 92). It seems likely from work on longitudinal SM of guinea pig ileum that entering calcium may release further calcium from sites which, during the period of observation, have frequently discharged calcium sparks and have been referred to as frequent-discharge sites (FDSs) (69). These may be the same sites as those referred to as "hot spots," where Ca2+ i first rises in the cell during the upstroke of the action potential (91). There are several FDSs, or hot spots, in any confocal plane through the cell, and it is from these that calcium waves spread throughout the cell (69, 91). The velocity of the calcium wave (30-260 mms-1) implies the presence of CICR since it is too high to be explained by simple diffusion; however, the calcium release sites involved in the calcium wave were not previously discharged by the entering calcium, yet are discharged by calcium release from an adjacent store site during calcium wave propagation (22).

Estimates of intracellular calcium wave propagation velocity perpendicular to the plasmalemma in single contracted SM cells of the guinea pig small intestine, using the line-scan mode of confocal microscopy, gave values in the range 50-75 mms-1 at room temperature (69; TB Bolton & DV Gordienko, unpublished results). In relaxed cells, no part of the cell is more than about 2 mm from the plasmalemma; this situation changes drastically upon contraction, and the question arises whether the SM cell has some special feature of the arrangement of the SR calcium stores such that rapid radial calcium wave propagation can still occur when the cell is strongly contracted. Under some conditions, for example when the muscarinic receptor is activated, intracellular calcium waves may conceivably influence membrane electrical activity through ion channels (K+, Cl-, or cation-selective) modulated or activated by calcium (115). These results and others indicate that, on occasions, not only do plasmalemmal electrical events trigger intracellular calcium waves but these in turn may also alter plasmalemmal electrical activity in the SM cell.

In SM cells, calcium waves that propagated through the cell could often be seen to originate from sites at which sparks were discharged (69). Although it is attractive to suppose that calcium waves and more general increases in calcium concentrations in the cell are composed of multiple elementary events (28), this is difficult to test since sparks can be discerned only when the rise in calcium concentration during a wave is small or modest. The spark probably represents a brief opening of one or a small cluster of ryanodine channels, which release calcium from the SR (34). Open times of channels are generally not constant but are exponentially distributed with one (or perhaps more than one) mean open time; therefore, it is odd that the sparks should be relatively constant in size. Clearly, some mechanism exists that confers this property; it could involve a threshold and an all-or-none (positive-feedback) process. When conditions change, such as they might during a calcium wave when the ionized-calcium concentration in the vicinity of the channel greatly increases, the mean open time may increase or more complex changes in channel kinetics may occur. Unfortunately, it is at just such times that it is difficult to visualize the component sparks, if they exist, and under these conditions calcium efflux through the open channel may be greater, perhaps proportional to the increase in channel open time, although with large increases in calcium efflux the calcium gradient might be expected to decline. RyR channels from skeletal and cardiac muscle increase their probability of the open state when Ca2+ is increased; whether the mean open time remains constant but the frequency of opening increases (as would be predicted if the spark were the elemental or quantal event underlying all SR calcium releases) has not been resolved (118, 191).

SARCOPLASMIC RETICULUM

RYANODINE RECEPTOR/CALCIUM RELEASE CHANNEL

Three isoforms of the RyR have been cloned and sequenced. Several alternatively spliced forms are known for each isoform. All have been described to be present in SMs, although the identity of the RyR types in individual SMs is just now beginning to be explored (66, 67, 123, 154). The RyR includes a cation channel which, after isolation and reconstitution in bilayers, was found to be 7.4 times more permeable to calcium than to potassium (234). Two types of RyR function are believed to exist: In skeletal muscle, a direct coupling of membrane depolarization to RyR channel opening is brought about by an association between a voltage- and dihydropyridine-sensitive calcium channel and the RyR; in cardiac muscle, a process of CICR occurs whereby calcium entering through these calcium channels triggers further calcium release through RyRs from the SR stores (203, 250). At present, such evidence as exists favors the notion that the situation in SM resembles that in cardiac muscle; however, a direct coupling such as that in skeletal muscle has by no means been eliminated as a possibility in all SMs, perhaps especially those which have been shown to have large inward sodium currents (see above).

Spliced variants of the isoforms designated RyR1, RyR2, and RyR3 have been identified in various SMs including esophagus, stomach, and small intestine (presumably in the SM of these organs). There is likely to be a tissue-specific distribution of these isoforms, but the physiological significance of this is not yet apparent (67, 119, 128, 154). RyRs are distributed on both superficial and deep SR (123).

Few electrophysiological studies exist concerning the behavior in bilayers of the isolated RyR channel from SMs (78, 239), but the evidence suggests that the channel probably behaves similarly to those from cardiac and skeletal muscles, where ryanodine and its analogs cause the channel to open and then be fixed in a partially open state or, at higher concentrations, to be blocked (208). Some SMs such as myometrium do not respond to caffeine by releasing calcium (124, 181, 182); this has been suggested to result from the expression of RyR3, which was observed to be insensitive to caffeine (66; but see 135).

Caffeine or ryanodine can act on the RyR to deplete or reduce the amount of calcium in the stores and block CICR (246, 247), slowing the recovery of Ca2+ i following a calcium load (61). Application of ryanodine, which opens calcium channels in the SR (83), or inhibition of SERCA by cyclopiazonic acid (144, 169, 213) or thapsigargin (169; but see 134) generally causes a rise in Ca2+ i and often in tension (213) in SM cells. It seems likely that the SR calcium pump is continuously active, perhaps especially if channels are opened in the SR through which calcium can escape to increase Ca2+ i in its vicinity (199). %%%Treatment%%% with ryanodine and then caffeine results in a persistent increase in Ca2+ i and tension in SM of gastric antrum (35); this %%%treatment%%% probably fixes
the RyR channels in the open state so that no calcium can be stored. Readmission of calcium to SMs where the calcium stores have been depleted causes contraction which is delayed compared to when the calcium stores are
full, presumably because calcium is first taken up to fill the empty stores and this initially reduces the amounts reaching the contractile proteins (82, 214). Superficial stores fill more rapidly than deeper ones (27, 64). However, %%%treatment%%% with caffeine or ryanodine to deplete SR calcium
stores does not accelerate the removal of a calcium load in toad gastric myocytes (133), and a similar result was obtained, after %%%treatment%%%
with cyclopiazonic acid or thapsigargin, which should inhibit filling of the SR stores (134).

The postulated vectorial transport of calcium by the plasmalemma (116, 214) presumably depends on calcium being present in the superficial SR and its continual extrusion from this into the 10-nm space between the plasmalemma (or caveolar) membrane and superficial SR outer membrane; from
here it is suggested to bind to the Na+/Ca2+ exchanger and to be extruded to the exterior. When the calcium stores under the plasmalemma are rendered inoperative, it would be expected that the total capacity of processes to remove calcium from the cell would be reduced, and the Ca2+ i deep in the cell (which represents an equilibrium between these processes and calcium entering the cell) would be expected to rise. However, the Ca2+ i immediately below the plasmalemma, between it and the superficial

SR, would be predicted to fall when the SR calcium store is depleted, since vectorial calcium transport to the exterior will cease; the predicted fall in subplasmalemmal Ca^{2+} i provides an explanation for the reduction in calcium-activated potassium current evoked upon depolarization when ryanodine (204), cyclopiazonic acid (98), or thapsigargin (61) is applied to SM cells, as well as the depolarization of the resting potential (125, 213) if this current normally makes a contribution. Conversely, an increase in this current is seen when SERCA is stimulated by nitric oxide, sodium nitroprusside, or sin-1 (98), which are believed to increase cGMP; membrane-permeable analogs of cGMP have a similar effect. If calcium-activated potassium channels can make a contribution to the resting membrane potential, they also provide an explanation for the relaxation caused by sodium nitroprusside and other nitric oxide donors (68, 168, 169). However, the relaxant effect of b-receptor activation is unaffected by ryanodine depletion of the calcium stores, suggesting that cAMP does not modulate SERCA (83).

Some observations are not consistent with the vectorial transport of calcium via superficial SR stores and Na/Ca exchanger to the exterior. Following a calcium load (induced by opening of voltage-dependent calcium channels) applied to single voltage-clamped toad gastric SM cells, the rate of fall of Ca^{2+} i is not affected by cyclopiazonic acid, thapsigargin, caffeine, or ryanodine (133, 134). It is, however, decreased under conditions where the ability of the Na/Ca exchanger to extrude calcium would be impaired, such as when the sodium gradient is reversed or abolished. These results argue that Na/Ca exchange is important quantitatively in removing a calcium load, at least in some SMs (but not guinea pig colonic SM, 132), and that most of the calcium it extrudes does not pass obligatorily through the superficial SR calcium stores.

When the calcium stores are empty, calcium entry may increase owing to activation of a calcium entry pathway (calcium release-activated channels), which is insensitive to organic calcium entry blockers. A similar effect can be produced if calcium stores are depleted by activating receptors, which increases IP3 production, or if cyclopiazonic acid or thapsigargin is used to inhibit SERCA (148, 164, 169, 227).

Mitochondria also play a significant role in the calcium economy of the SM cell. They take up calcium following a calcium load applied to the cell, and this process is slowed by mitochondrial inhibitors or inhibitors of calmodulin-dependent PKII (42, 70, 133, 134).

INOSITOL TRISPHOSPHATE CALCIUM RELEASE CHANNEL

When many G-protein-linked receptors are activated, IP3 is formed in increased amounts through stimulation of PLC activity. Three types of IP3 receptor have been reported to be present in SM (95, 143). IP3 receptors are distributed on both superficial and deep SR (157), and in intestinal SM about 10 times more IP3 receptors than RyRs were found by cell fractionation and binding studies (232). The action of IP3 on its receptor is blocked by heparin, which does not block and may potentiate, the opening of RyR receptors. In bilayers, the IP3 receptor calcium channel has a conductance in quasi-physiological calcium gradients, of 30-50 pS, depending on whether a lipid bilayer was seeded with purified receptor (131) or with a microsomal preparation containing the receptor (17). SM microsomes from canine aorta gave a lower value under different conditions (43). It has been calculated that the current through the channel under physiological conditions might be 0.5 pA (17). Its opening in response to IP3 is potentiated by low and inhibited by high concentrations of calcium (17, 18, 88). Cytoplasmic calcium and IP3 synergize in opening the IP3-receptor channel (79). ATP also potentiates the opening of the channel (89). The potentiating effect of SR luminal Ca^{2+} on IP3-mediated calcium release may contribute to the phenomenon whereby the long-lasting application of submaximally effective concentrations of IP3 does not release all stored calcium (so-called quantal calcium release) even if SERCA is inhibited by thapsigargin and the Ca^{2+} i is heavily buffered (166). In such experiments, it is necessary to be certain that all SR calcium pumps have been completely inhibited, because the simultaneous operation of the SERCA pump with the opening of calcium channels in the SR can produce an equilibrium situation (199); this has been suggested to provide an explanation for the phenomenon of quantal release in the case of the RyR. A number of other explanations have been proffered for quantal release (25, 166). Further properties of the IP3 receptor channel have been reviewed (17).

In single cells, oscillations of Ca^{2+} i can be observed in response to activation of G-protein-linked receptors that generate IP3. These oscillations can also be observed when the membrane potential of single cells is voltage clamped; therefore, the oscillation presumably does not involve potential-dependent plasmalemma channels but originates in the interior of the cell and involves the SR. The oscillations in response to muscarinic receptor activation can be monitored by the change in size of the cationic current, which is modulated by Ca^{2+} i. Photolytic release of IP3 from an inert precursor at different times with respect to the oscillations of Ca^{2+} i suggested that IP3 was able to release calcium from the SR when Ca^{2+} i was low (and the level of calcium in the SR high) and was not able to release it when Ca^{2+} i was high (and the level of calcium in the SR lower) (107, 249). It seemed possible that while IP3 production may be steady, the release of a small amount of calcium from the SR results in a potentiation of the action of IP3 on the SR and further calcium release; a regenerative system is thereby formed which may release most of the SR calcium content, at which point calcium release will cease and Ca^{2+} i will fall as the SR fills (107). Essentially similar conclusions have been reached on the basis of other types of experiment (90).

It has been suggested that IP3 receptors occur in clusters and that some form of concerted opening of the channels within a cluster occurs to produce "puffs;" smaller increases in Ca^{2+} i that were detected ("blips") could represent openings of single IP3 receptor calcium channels (165). Binding studies indicate that in intestinal SM there are about 10 times more IP3 receptors than RyRs (232). However, the relationship between these and their locations on the SR or elsewhere is imperfectly known or understood. In guinea pig longitudinal intestinal muscle, where IP3-mediated oscillations in Ca^{2+} i readily occur in response to activation of various plasmalemma receptors, similar oscillations are not seen in response to caffeine (107, 249). The STOC frequency may be increased by lower concentrations of caffeine, and STOCs may be regarded as a type of (irregular) oscillation; more regular oscillations occur in other SMs in response to caffeine (101, 122). Possibly, calcium potentiates the opening of RyR channels at a higher concentration than is required to potentiate the opening of IP3 calcium channels in the SR.

SUMMARY AND CONCLUSIONS

Contraction or tension generation by SMs generally involves some form of depolarization of the membrane, which admits more calcium into the cell through voltage-dependent calcium channels; hyperpolarization has the opposite effect and is associated with relaxation of existing tension. In gastrointestinal SMs, depolarization occurs through the discharge of action potentials or slow waves, although slower depolarization may occur on occasion. Receptor activation triggers other mechanisms that raise Ca^{2+} i: the most important of these is the PLC/IP3/DAG system; calcium may also enter through channels opened by receptor activation or stretch. Receptors for excitatory signal molecules are mostly G protein coupled and may modulate ion channel activity directly (and thus electrical activity) or via phosphorylation. In addition, a number of receptors are known to activate tyrosine kinases directly without the intervention of G proteins and to interact with G protein-coupled systems. Although a change in Ca^{2+} i is the most important mechanism for the control of tension, other G protein- and kinase-mediated mechanisms are able to modulate or even perhaps initiate tension generation, or to inhibit it, producing relaxation.

The plasmalemma of the SM cell appears to have two domains: One of these acts as an anchor site for the contractile proteins, and the other may be the location of most of the ion channels and ion pumps; the latter has the caveolae and is related to the SR. These two domains exist as parallel longitudinal stripes on the plasmalemma. SR is reported to be superficially located in phasic SMs but to be more extensive and located centrally in tonic SMs, which do not readily generate action potentials and generally show only slow changes in potential.

The rise in Ca^{2+} i produced by calcium entry into the cell, or perhaps by the action of IP3 produced as a result of receptor activation, may trigger further calcium release from calcium stores in the cell by a CICR process. The main calcium stores are believed to exist in the SR, although mitochondria also have a storage role. The SR has both RyRs and IP3 receptors. Spontaneous calcium discharges (sparks) occur in certain preferred locations, the FDSs; sparks give rise to STOCs and/or STICs. Recent evidence suggests that in phasic SMs generating action potentials and/or slow waves, RyRs are located in relation to calcium fluxes such that, during calcium entry through voltage-dependent calcium channels, a high Ca^{2+} i is achieved in their vicinity, resulting in CICR. Calcium entering the cell through voltage-dependent calcium channels triggers calcium release first from hot spots, which may be identical to FDSs; from these, a calcium wave spreads to other parts of the cell by CICR. IP3 receptors, when activated, may create sufficient calcium flux from the SR for CICR also to occur.

The level of Ca^{2+} i can feed back to affect plasmalemmal electrical

activity by increasing the probability of opening of calcium-activated K+, Cl+, and cation channels. There is also evidence that the state of filling of the calcium stores in the SR may modulate calcium-activated K+ channel activity in the plasmalemma and that when SR calcium storage is increased, the outward BKCa current is also increased. These effects may be manifestations of the vectorial transport of calcium by the SR to the exterior across the narrow gap between it and the plasmalemma, although not
all observations are consistent with this interpretation.

Added material

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guinea-pig small intestine. J. Physiol. 481:97-109

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4/7/66 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal
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12769001 PASCAL No.: 96-0484053
Effects of thyroid hormone on left ventricular performance and regulation on contractile and Ca SUP 2 SUP + -cycling proteins in the baboon : Implications for the force-frequency and relaxation-frequency relationship
KHOURY S F; HOIT B D; DAVE V; PAWLOSKI-DAHM C M; SHAO Y; GABEL M;
PERIASAMY M; WALSH R A
Division of Cardiology, University of Cincinnati (Ohio) Medical Center, United States
Journal: Circulation research, %%%1996%%%, 79 (4) 727-735
ISSN: 0009-7330 CODEN: CIRUAL Availability: INIST-7216; 354000066298290100
No. of Refs.: 51 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
The transcriptional, posttranscriptional, and related functional effects of thyroid hormone on primate myocardium are poorly understood. Therefore, we studied the effects of thyroid hormone on sarcoplasmic reticulum (SR) Ca SUP 2 SUP + -cycling proteins and myosin heavy chain (MHC) composition at the steady state mRNA and protein level and associated alterations of left ventricular (LV) performance in 8 chronically instrumented baboons. The force-frequency and relaxation-frequency relations were assessed as the response of LV isovolumic contraction (dP/dt SUB m SUB a SUB x) and relaxation (Tau), respectively, to incremental atrial pacing. Both the %%%heart%%% rate at which dP/dt SUB m SUB a SUB x was maximal and Tau was minimal (critical %%%heart%%% rates) in response to pacing were increased significantly after thyroid hormone. Postmortem LV tissue from 5 thyroid-%%%treated%%% and 4 additional control baboons was assayed for steady state mRNA levels with cDNA probes to MHC isoforms and SR Ca SUP 2 SUP + -cycling proteins. Steady state SR Ca SUP 2 SUP + -ATPase and %%%phospholamban%%% mRNA increased in the hyperthyroid state, and alpha -MHC mRNA appeared de novo, whereas beta -MHC mRNA decreased. Western analysis (4 thyroid-%%%treated%%% and 4 control baboons) showed directionally similar changes in MHC isoforms and a slight increase in SR Ca SUP 2 SUP + -ATPase. In contrast, there was a statistically nonsignificant decrease in %%%phospholamban%%% protein, which resulted in a significant 40% decrease in the ratio of %%%phospholamban%%% to SR Ca SUP 2 SUP + -ATPase. Thus, thyroid hormone increases the transcription of Ca SUP 2 SUP + -cycling proteins and shifts MHC isoform expression in the primate LV. Our data suggest that both transcriptional and posttranslational mechanisms determine the levels of these proteins in the hyperthyroid primate %%%heart%%% and mediate, in part, the observed enhanced basal and frequency-dependent LV performance.

4/7/67 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07073846 91314781 PMID: 1858918
L-propionylcarnitine increases postischemic blood flow but does not affect recovery of energy charge.
Sassen L M; Bezstarosti K; Van der Giessen W J; Lamers J M; Verdouw P D
Laboratory for Experimental Cardiology, Thoraxcenter, Erasmus University
Rotterdam, The Netherlands.
American journal of physiology (UNITED STATES) Jul %%%1991%%%, 261 (1 Pt 2) pH172-80, ISSN 0002-9513 Journal Code: 0370511
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Effects of pretreatment with L-propionylcarnitine (50 mg/kg, n = 9) or saline (n = 10) were studied in open-chest anesthetized pigs, in which ischemia was induced by decreasing left anterior descending coronary artery blood flow to 20% of baseline. After 60 min of ischemia, myocardium was reperfused for 2 h. In both groups, flow reduction abolished contractile function of the affected myocardium and caused similar decreases in ATP (by 55%) and energy charge [(ATP + 0.5ADP)/(ATP + ADP + AMP); decrease from 0.91 to 0.60], mean arterial blood pressure (by 10-24%), the maximum rate of rise in left ventricular pressure (by 26-32%), and cardiac output (by 20-30%). During reperfusion, "no-reflow" was attenuated by L-propionylcarnitine, because myocardial blood flow returned to 61 and 82% of baseline in the saline- and L-propionylcarnitine-%%%treated%%% animals, respectively. Cardiac output of the saline-%%%treated%%% animals further decreased (to 52% of baseline), and systemic vascular resistance increased from 46 +/- 3 to 61 +/- 9 mmHg.min.l-1, thereby maintaining arterial blood pressure. In L-propionylcarnitine-%%%treated%%% pigs, cardiac output remained at 75% of baseline, and systemic vascular resistance decreased from 42 +/- 3 to 38 +/- 4 mmHg.min.l-1. In both groups, energy charge but not the ATP level of the ischemic-reperfused myocardium tended to recover, whereas the creatine phosphate level showed significantly more recovery in saline-%%%treated%%% animals. We conclude that L-propionylcarnitine partially preserved vascular patency in ischemic-reperfused porcine myocardium but had no immediate effect on "myocardial stunning." Potential markers for long-term recovery were not affected by L-propionylcarnitine.
Record Date Created: 19910823
Record Date Completed: 19910823

4/7/68 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06186843 89202447 PMID: 2523077
Regulation of myocardial Ca2+-ATPase and %%%phospholamban%%% mRNA expression in response to pressure overload and thyroid hormone.
Nagai R; Zarain-Herzberg A; Brandl C J; Fujii J; Tada M; MacLennan D H; Alpert N R; Periasamy M
Department of Physiology and Biophysics, University of Vermont College of Medicine, Burlington 05405.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Apr %%%1989%%%, 86 (8) p2966-70, ISSN 0027-8424 Journal Code: 7505876
Contract/Grant No.: P.O.1 HL 28001-01; HL; NHLBI; R.O. 139303; PHS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The sarcoplasmic reticulum (SR) and the contractile protein myosin play an important role in myocardial performance. Both of these systems exhibit plasticity-i.e., quantitative and/or qualitative reorganization during development and in response to stress. Recent studies indicate that SR Ca2+ uptake function is altered in adaptive cardiac hypertrophy and %%%failure%%% . The molecular basis (genetic and phenotypic) for these changes is not understood. In an effort to determine the underlying causes of these changes, we characterized the rabbit cardiac Ca2+-ATPase phenotype

by molecular cloning and ribonuclease A mapping analysis. Our results show that the %%%heart%%% muscle expresses only the slow-twitch SR Ca2+-ATPase
isoform. Second, we quantitated the steady-state mRNA levels of two major
SR Ca2+ regulatory proteins, the Ca2+-ATPase and %%%phospholamban%%%, to
see whether changes in mRNA content might provide insight into the basis for functional modification in the SR of hypertrophied hearts. In response to pressure overload hypertrophy, the relative level of the slow-twitch/cardiac SR Ca2+-ATPase mRNA was decreased to 34% of control at
1 week. The relative Ca2+-ATPase mRNA level increased to 167% of control
after 3 days of %%%treatment%%% with thyroid hormone. In contrast, in
hypothyroid animals, the relative Ca2+-ATPase mRNA level decreased to 51%
of control at 2 weeks. The relative level of %%%phospholamban%%% mRNA was
decreased to 36% in 1-week pressure overload. Hyperthyroidism induced a decrease to 61% in the %%%phospholamban%%% mRNA level after 3 days of
%%%treatment%%%, while hypothyroidism had virtually no effect on %%%phospholamban%%% mRNA levels. These data indicate that the expression of
SR Ca2+-ATPase and %%%phospholamban%%% mRNA may not be coordinately
regulated during myocardial adaptation to different physiological conditions.
Record Date Created: 19890524
Record Date Completed: 19890524

4/7/69 (Item 1 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

131286418 CA: 131(21)286418n PATENT
A method for the prevention and treatment of stunned myocardium using benzopyranones, quinolinones, and other phospholamban inhibitors
INVENTOR(AUTHOR): Haikala, Heimo; Kaheinen, Petri; Levijoki, Jouko; Kaivola, Juha; Ovaska, Martti; Pystynen, Jarmo
LOCATION: Finland
ASSIGNEE: Orion Corp.
PATENT: United States ; US 5968959 A DATE: 19991019
APPLICATION: US 188707 (19981110) *US 990146 (19971212)
PAGES: 29 pp., Cont.-in-part of U. S. Ser. 990,146, abandoned. CODEN: USXXAM LANGUAGE: English CLASS: 514345000; A61K-031/44A; A61K-031/41B;
A61K-031/35B
SECTION:
CA227017 Heterocyclic Compounds (One Hetero Atom)
CA201XXX Pharmacology
CA263XXX Pharmaceuticals
IDENTIFIERS: stunned myocardium therapy benzopyranone quinolinone prepn
phospholamban inhibitor
DESCRIPTORS:
Heart,disease...
angina pectoris, unstable, treatment; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium
Phospholambans...
inhibitors; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium
Reperfusion...
injury, treatment of; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium
Heart,disease...
stunning; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium
Heart,disease...
valve, treatment; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium
CAS REGISTRY NUMBERS:
3722-45-0P 7758-73-8P 219551-85-6P 219551-86-7P 219551-88-9P
219551-89-0P 219551-91-4P 219551-92-5P 219551-94-7P
219551-96-9P
219551-98-1P 219551-99-2P 219552-01-9P 219552-03-1P
219552-04-2P
219552-05-3P 219552-06-4P 219552-07-5P 219552-08-6P
219552-10-0P
219552-11-1P 219552-12-2P 219552-24-6P 219552-25-7P
219552-26-8P
219552-28-0P 219552-29-1P 219552-31-5P 219552-32-6P
219552-34-8P
219552-35-9P 219552-37-1P 219552-38-2P 219552-40-6P
219552-41-7P
219552-42-8P 219552-43-9P 219552-45-1P 219552-47-3P
219552-48-4P
219552-49-5P 219552-51-9P 219552-52-0P 219552-53-1P
219552-54-2P
221328-21-8P 221328-22-9P 221328-23-0P intermediate; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium
219551-84-5P 219551-87-8P 219551-90-3P 219551-93-6P 219551-95-8P
219551-97-0P 219552-00-8P 219552-02-0P 219552-09-7P
219552-15-5P
219552-22-4P 219552-23-5P 219552-27-9P 219552-30-4P
219552-33-7P
219552-36-0P 219552-39-3P 219552-44-0P 219552-50-8P
219552-55-3P
219552-56-4P 219552-57-5P 221328-10-5P 221328-20-7P prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium
94-02-0 100-39-0 105-36-2 108-73-6 141-30-0 352-11-4 620-79-1
1540-32-5 1617-17-0 1655-07-8 1694-31-1 5337-63-3 10272-07-8
13658-19-0 24106-86-3 36600-72-3 61713-40-4 88022-93-9
144192-31-4
reactant; prepn. of benzopyranones and quinolinones as phospholamban inhibitors for the prevention and treatment of stunned myocardium

4/7/70 (Item 2 from file: 399)
DIALOG(R)File 399:CA SEARCH(R)

130163185 CA: 130(13)163185f PATENT
Evaluation of, delivery of, and use of agents to treat heart disorders
INVENTOR(AUTHOR): Hajjar, Roger J.; Rosenzweig, Anthony; Guerrero, Luis
LOCATION: USA
ASSIGNEE: The General Hospital Corporation
PATENT: PCT International ; WO 9904636 A1 DATE: 19990204
APPLICATION: WO 98US14968 (19980720) *US 53356 (19970722)
PAGES: 51 pp. CODEN: PIXXD2 LANGUAGE: English CLASS: A01N-063/00A;
A01N-043/04B; C12Q-001/68B; C12N-015/64B; C12N-005/00B; C07H-021/04B
DESIGNATED COUNTRIES: CA; JP DESIGNATED REGIONAL: AT; BE; CH; CY; DE; DK
; ES; FI; FR; GB; GR; IE; IT; LU; MC; NL; PT; SE
SECTION:
CA201008 Pharmacology
CA263XXX Pharmaceuticals
IDENTIFIERS: heart disorder phospholamban nucleic acid transfer
DESCRIPTORS:
Phospholambans...
and phospholamban-expressing nucleic acid; evaluation, delivery, and use of agents to treat heart disorders
cDNA...
antisense; evaluation, delivery, and use of agents to treat heart disorders
Sarcoplasmic reticulum...
calcium ATPase; evaluation, delivery, and use of agents to treat heart disorders
Antisense DNA...
cDNA; evaluation, delivery, and use of agents to treat heart disorders
Anti-ischemic agents... Cardiac contraction... Cardiovascular agents...

Coronary artery... Drug delivery systems... Drug screening... Gene therapy ... Heart diseases... Heart failure... Heart transplant... Myocardial ischemia... Myocyte(heart)... Nucleic acids... Transplant rejection... Virus vectors...
evaluation, delivery, and use of agents to treat heart disorders
Peptides,biological studies...
nucleic acid directing expression of; evaluation, delivery, and use of agents to treat heart disorders
Transgenes...
phospholamban pathway protein-encoding; evaluation, delivery, and use of agents to treat heart disorders
Genes...
somatic gene transfer; evaluation, delivery, and use of agents to treat heart disorders
Transformation(genetic)...
transgenic animal; evaluation, delivery, and use of agents to treat heart disorders
Adenoviridae...
vector; evaluation, delivery, and use of agents to treat heart disorders
CAS REGISTRY NUMBERS:
7440-70-2 biological studies, evaluation, delivery, and use of agents to treat heart disorders
9000-83-3 calcium-; evaluation, delivery, and use of agents to treat heart disorders

4/7/71 (Item 1 from file: 434)
DIALOG(R)File 434:SciSearch(R) Cited Ref Sci
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08563159 Genuine Article#: L7796 Number of References: 55
Title: EFFECTS OF PROLONGED PHENYLEPHRINE INFUSION ON CARDIAC ADRENOCEPTORS
AND CALCIUM CHANNELS
Author(s): GENGO PJ; BOWLING N; WYSS VL; HAYES JS
Corporate Source: ELI LILLY & CO,LILLY CORP CTR,LILLY RES LABS,DEPT CARDIOVASC PHARMACOL/INDIANAPOLIS//IN/46285
Journal: JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, %%%1988%%%
, V244, N1, P100-105
Language: ENGLISH Document Type: ARTICLE

4/7/72 (Item 2 from file: 434)
DIALOG(R)File 434:SciSearch(R) Cited Ref Sci
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07097323 Genuine Article#: A1000 Number of References: 76
Title: BETA-ADRENERGIC-RECEPTOR BLOCKADE OF FELINE MYOCARDIUM - CARDIAC
MECHANICS, ENERGETICS, AND BETA-ADRENOCEPTOR REGULATION
Author(s): COOPER G; KENT RL; MCGONIGLE P; WATANABE AM
Corporate Source: TEMPLE UNIV,HLTH SCI CTR,SCH MED,DEPT INTERNAL
MED,CARDIOL SECT/PHILADELPHIA//PA/19140; TEMPLE UNIV,HLTH SCI CTR,SCH
MED,DEPT PHYSIOL/PHILADELPHIA//PA/19140; TEMPLE UNIV,HLTH SCI CTR,SCH
MED,DEPT PHARMACOL/PHILADELPHIA//PA/19140; UNIV PENN,SCH MED,DEPT
PHARMACOL/PHILADELPHIA//PA/19104; INDIANA UNIV,SCH MED,KRANNERT INST
CARDIOL,DEPTMED/INDIANAPOLIS//IN/46223; INDIANA UNIV,DEPT
PHARMACOL/INDIANAPOLIS//IN/46223
Journal: JOURNAL OF CLINICAL INVESTIGATION, %%%1986%%%, V77, N2, P441-455
Language: ENGLISH Document Type: ARTICLE
? ds

Set Items Description
S1 1736 HEART AND (DISEAS? OR FAILURE?) AND PHOSPHOLAMBAN
S2 927 RD S1 (unique items)
S3 518 S2 AND PY<2000
S4 72 S3 AND (TREAT? OR AMELORIAT?)
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518 S3
1049676 CONTRACT?
S5 265 S3 AND CONTRACT?
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265 S5
72 S4
S6 225 S5 NOT S4
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225 S6
2250241 CALCIUM
S7 172 S6 AND CALCIUM
? s s7 and ATP
172 S7
547580 ATP
S8 14 S7 AND ATP
? t s8/7/all
>>>Format 7 is not valid in file 143

8/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11768647 BIOSIS NO.: 199900014756
Frequency dependent force generation correlates with sarcoplasmic %%%calcium%%% ATPase activity in human myocardium.
AUTHOR: Frank K; Boelck B; Bavendiek U; Schwinger R H G(a)
AUTHOR ADDRESS: (a)Lab. Muscle Res. Mol. Cardiol., Klinik III Innere Med.,
Univ. Koeln, Joseph-Stelzmann-Str. 9, 50**Germany
JOURNAL: Basic Research in Cardiology 93 (5):p405-411 Oct., %%%1998%%%
ISSN: 0300-8428
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Objective: In congestive %%%heart%%% %%%failure%%% both a
decreased function of the sarcoplasmic Ca2+-ATPase and negative force-frequency relationship have been shown. This study aimed to investigate a possible relationship between frequency potentiation, sarcoplasmic Ca2+-ATPase activity, and SERCA2 protein expression in human
myocardium. Methods: Frequency potentiation was studied in electrically stimulated, isometric, left ventricular papillary muscle strip preparations (37 degreeC, 0.5 3.0 Hz) from terminally failing (NYHA IV; n = 5, dilated cardiomyopathy) and nonfailing (donor hearts, n = 5) human myocardium. In the identical samples the Ca2+-ATPase activity (NADH coupled assay) and the protein expression of sarcoplasmic Ca2+-ATPase (SERCA2), %%%phospholamban%%%, and calsequestrin (western blot) were determined. The frequency dependent change in the force of %%%contraction%%% and Vmax of the Ca2+-ATPase activity and the protein
expression of SERCA2 were correlated with each other. Results: In terminally failing myocardium the force-frequency relationship was negative (2.0 Hz vs. 0.5 Hz: -0.2 +- 0.1 DELTAmN) contrasting a positive rate dependent potentiation of force in nonfailing tissue (2.0 Hz vs. 0.5 Hz: +0.8 +- 0.2 DELTAmN; p < 0.01). In failing myocardium the corresponding maximal sarcoplasmic Ca2+-ATPase activity (Vmax) was reduced significantly compared to nonfailing myocardium (174 +- 24 vs. 296 +- 31 nmol %%%ATP%%%/mgcntdotmin, p < 0.01). The protein expression
of SERCA2, %%%phospholamban%%%, and calsequestrin remained unchanged in
failing myocardium. The maximal Ca2+-ATPase activity significantly correlated with the frequency dependent change in force of %%%contraction%%% (2 Hz vs. 0.5 Hz: r = 0.88, p = 0.001; 3 Hz vs. 0.5 Hz: r = 0.84, p = 0.004). No correlation between protein expression of SERCA2 and Ca2+ATPase activity or change in force of %%%contraction%%% was observed. Conclusion: Due to a significant correlation between

sarcoplasmic Ca2+ATPase activity and frequency potentiation, the negative rate dependent force potentiation in human %%%heart%%% %%%failure%%% could be at least in part be attributed to decreased function of the sarcoplasmic Ca2+-ATPase.

8/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09436922 BIOSIS NO.: 199497445292
Ca-2+-transporting ATPAse, %%%phospholamban%%%, and calsequestrin levels in nonfailing and failing human myocardium.
AUTHOR: Movsesian Matthew A(a); Karimi Mohsen; Green Karen; Jones Larry R
AUTHOR ADDRESS: (a)Cardiol. Div., Room 4A-100, Univ. Utah Health Sci. Center, 50 N. Medical Dr., Salt Lake City, UT**USA
JOURNAL: Circulation 90 (2):p653-657 %%%1994%%%
ISSN: 0009-7322
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Observations of abnormalities in the diastolic components of intracellular Ca-2+ transients in failing human left ventricular myocardium have raised the possibility that reductions in the level or function of sarcoplasmic reticulum proteins involved in Ca-2+ transport contribute to the pathophysiology of dilated cardiomyopathy in humans. Functional assays, however, have revealed no differences in %%%ATP%%%-dependent Ca-2+ transport or its modulation by %%%phospholamban%%% in sarcoplasmic reticulum-enriched microsomes prepared from nonfailing and failing human left ventricular myocardium. The purpose of the present study was to quantify protein levels of Ca-2+-transporting ATPase, %%%phospholamban%%%, and calsequestrin directly in nonfailing and failing human left ventricular myocardium. Methods and Results: Total protein extracts were prepared from nonfailing left ventricular myocardium from the hearts of unmatched organ donors with normal left ventricular %%%contractility%%% (n = 6) and from failing left ventricular myocardium from the excised hearts of transplant recipients with class IV %%%heart%%% %%%failure%%% resulting from idiopathic dilated cardiomyopathy (n = 6). Ca-2+-transporting ATPase, %%%phospholamban%%%, and calsequestrin contents were determined by quantitative immunoblotting with monoclonal and affinity-purified polyclonal antibodies. The levels of the three proteins were identical in nonfailing and failing human left ventricular myocardium. Conclusions: These results indicate that protein levels of Ca-2+-transporting ATPase, %%%phospholamban%%%, and calsequestrin are not diminished in failing human left ventricular myocardium and that downregulation of the Ca-2+-transporting ATPase and %%%phospholamban%%% is not part of the molecular pathophysiology of dilated cardiomyopathy in humans.

8/7/3 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

04488422 Genuine Article#: TG292 Number of References: 49
Title: UNCHANGED PROTEIN-LEVELS OF SERCA-II AND %%%PHOSPHOLAMBAN%%% BUT REDUCED CA2+ UPTAKE AND CA2+-ATPASE ACTIVITY OF CARDIAC SARCOPLASMIC-RETICULUM FROM DILATED CARDIOMYOPATHY PATIENTS COMPARED WITH PATIENTS WITH NONFAILING HEARTS
Author(s): SCHWINGER RHG; BOHM M; SCHMIDT U; KARCZEWSKI P; BAVENDIEK U; FLESCH M; KRAUSE EG; ERDMANN E
Corporate Source: UNIV COLOGNE,MED KLIN 3,JOSEPH STELZMANN STR 9/D-50924 COLOGNE//GERMANY/; MAX DELBRUCK ZENTRUM MOLEK MED/D-13125 BERLIN//GERMANY/
Journal: CIRCULATION, %%%1995%%%, V92, N11 (DEC 1), P3220-3228
ISSN: 0009-7322
Language: ENGLISH Document Type: ARTICLE

Abstract: Background The aim of the present study was to investigate whether Ca2+ uptake into the sarcoplasmic reticulum (SR) is altered in failing human myocardium resulting from dilated cardiomyopathy.

Methods and Results Ca2+-ATPase (SERCA II) activity and Ca2+-dependent Ca-45(2+) uptake (oxalate supported, steady state) in isolated vesicles from the SR (VSR) and in crude membrane preparations (CSR) (free Ca2+, 0.01 to 100 mu mol/L) from nonfailing (donor hearts, n=13) and terminally failing (%%%heart%%% transplants, dilated cardiomyopathy, n=17) human myocardium were studied. In the same hearts, protein levels (Western blot analysis) and mRNA levels (Northern blot analysis) of SERCA II and %%%phospholamban%%% were measured, Increasing concentrations of Ca2+ were followed by an increased Ca2+-ATPase activity and Ca2+ uptake. Ca2+ uptake activity and Ca2+-ATPase activity in CSR preparations from failing myocardium were significantly reduced compared with nonfailing hearts (Ca2+-ATPase, 163+/-8 and 125+/-7 nmol %%%ATP%%%/mg protein per minute for nonfailing tissue and failing tissue in New York %%%Heart%%% Association [NYHA] class IV, respectively; Ca2+ uptake, 7.1+/-0.8 and 3.5+/-0.3 nmol/mg protein per minute in CSR from nonfailing and NYHA class IV hearts, respectively; P<.05). In contrast, no significant difference was measured in VSR. In the same preparations (CSR and VSR), both SERCA II and %%%phospholamban%%% levels (Western blot technique with monoclonal antibodies) were unchanged in failing compared with nonfailing tissue. mRNA expression relative to GAPDH mRNA for SERCA IIa and for %%%phospholamban%%% was significantly reduced in failing human myocardium (P<.05).

Conclusions These findings provide evidence that in failing human myocardium caused by dilated cardiomyopathy, protein levels of SERCA II and %%%phospholamban%%% are unchanged even though mRNA levels for SERCA II and %%%phospholamban%%% and the SERCA II function are reduced compared with nonfailing myocardium.

8/7/4 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci

03575402 Genuine Article#: PP071 Number of References: 59
Title: ENERGETIC MODULATION OF CARDIAC INOTROPISM AND SARCOPLASMIC RETICULAR CA2+ UPTAKE
Author(s): MALLET RT; BUNGER R
Corporate Source: UNIV N TEXAS,HLTH SCI CTR,DEPT PHYSIOL,3500 CAMP BOWIE BLVD/FT WORTH//TX/76107; UNIFORMED SERV UNIV HLTH SCI,F EDWARD HEBERT SCH MED,DEPT PHYSIOL/BETHESDA//MD/20814
Journal: BIOCHIMICA ET BIOPHYSICA ACTA-MOLECULAR CELL RESEARCH, %%%1994%%%
, V1224, N1 (OCT 20), P22-32
ISSN: 0167-4889
Language: ENGLISH Document Type: ARTICLE
Abstract: Myocardial %%%contractile%%% performance is a function of sarcoplasmic reticular Ca2+ uptake and release. Ca2+ handling is %%%ATP%%%-dependent and can account for up to 40% of total myocardial energy expenditure. We tested the hypothesis that the thermodynamics of the cytosolic adenylate system can modulate sarcoplasmic reticular Ca2+ handling and hence function in intact %%%heart%%%. Cellular energy level was experimentally manipulated by perfusing isolated working guinea-pig hearts with substrate-free medium or media fortified with lactate and/or pyruvate as the main energy substrate. Left ventricular %%%contractile%%% function was judged by stroke work and intraventricular dP/dt. Cytosolic energy level was indexed by measured creatine kinase reactants. Relative to 5 mM lactate, 5 mM pyruvate increased left ventricular stroke work, dP/dt(max), and dP/dt(min), while lowering left ventricular end-diastolic pressure at physiological

left atrial and aortic pressures. Pyruvate also doubled cytosolic phosphorylation potentials and increased [%%%ATP%%%]/[ADP] ratio: this
energetic enhancement distinguishes pyruvate from inotropic stimulation by catecholamines, which are known to decrease cytosolic energy level in perfused %%%heart%%%. Sarcoplasmic reticular Ca2+ handling was assessed in hearts prelabeled with Ca-45, subjected to Ca-45 washout in the presence of different cytosolic energy levels, then stimulated with 10 mM caffeine to release residual sarcoplasmic reticular Ca-45. When ryanodine (1 mu M) was applied to open Ca2+ channels and thereby released Ca-45 from the sarcoplasmic reticulum during washout, caffeine-stimulated Ca-45 release was decreased 96%, demonstrating that
virtually the entire caffeine-sensitive Ca-45 pool was located in the sarcoplasmic reticulum. In detailed comparisons of pyruvate-energized vs. substrate-free deenergized hearts, an inverse relationship between cytosolic energy level and caffeine-mobilized Ca-45 pool size was observed. Thus, caffeine-induced Ca-45 release was decreased 60% by pyruvate energization and increased 2.5-fold by substrate-free deenergization. Taken together, these results support the hypothesis that enhancement of myocardial inotropism by energy-yielding substrate is mediated by increased sarcoplasmic reticular Ca2+ loading/release. Thus we propose that the known control of sarcoplasmic reticular Ca2+ turnover by the protein kinase/%%%phospholamban%%% system can be modulated by cytosolic energy level.

8/7/5 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07456737 EMBASE No: 1998372296
Regulation of the Casup 2sup + gradient across the sarcoplasmic reticulum in perfused rabbit %%%heart%%%: A sup 1sup 9F nuclear magnetic resonance
study
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Circulation Research (CIRC. RES.) (United States) 02 NOV 1998, 83/9 (898-907)
CODEN: CIRUA ISSN: 0009-7330
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 44

Myocardial %%%contractility%%% depends on Casup 2sup + release from and
uptake into the sarcoplasmic reticulum (SR). The Casup 2sup + gradient between the SR matrix and the cytosol (SR Casup 2sup + gradient) is maintained by the SR Casup 2sup +-ATPase using the free energy available from hydrolysis of %%%ATP%%%. The activity of the SR Casup 2sup +-ATPase is
not only dependent on the energy state of the cell but is also kinetically regulated by SR proteins such as %%%phospholamban%%%. To evaluate the importance of thermodynamic and kinetic regulation of the SR Casup 2sup + gradient, we examined the relationship between the energy available from %%%ATP%%% hydrolysis (DeltaG(%%%ATP%%%)) and the energy required for
maintenance of the SR Casup 2sup + gradient (DeltaG(Ca2+SR)) during physiological and pathological manipulations that alter DeltaG(%%%ATP%%%)
and the phosphorylation state of %%%phospholamban%%%. We used our previously developed sup 1sup 9F nuclear magnetic resonance method to measure the ionized [Casup 2sup +] in the SR of Langendorff- perfused rabbit hearts. We found that addition of either pyruvate or isoproterenol resulted in an increase in left ventricular developed pressure and an increase in [Casup 2+](SR). Pyruvate increased DeltaG(%%%ATP%%%), and the
increase in the SR Casup 2sup + gradient was matched to the increase in DeltaG(%%%ATP%%%); DeltaG(%%%ATP%%%) increased from 58.3 +/- 0.5 to 60.4
+/- 1.0 kJ/mol (P < 0.05), and DeltaG(Ca2+SR) increased from 47.1+/-0.3 to 48.5+/-0.1 kJ/mol (P < 0.05). In contrast, the increase in the SR Casup 2sup + gradient in the presence of isoproterenol occurred despite a decline in DeltaG(%%%ATP%%%) from 58.3+/-0.5 to 55.8+/-0.6 kJ/mol. Thus, the data
indicate that the SR Casup 2sup + gradient can be increased by an increase in DeltaG(%%%ATP%%%), and that the positive inotropic effect of pyruvate can be explained by improved energy-linked SR Casup 2sup + handling, whereas the results with isoproterenol are consistent with removal of the kinetic limitation of %%%phospholamban%%% on the activity of the sarcoplasmic/endoplasmic reticulum Casup 2sup +-ATPase, which allows the SR
Casup 2sup + gradient to move closer to its thermodynamic limit. Ischemia decreases DeltaG(%%%ATP%%%), and this should also have an effect on SR Casup 2sup + handling. During 30 minutes of ischemia, Delta(%%%ATP%%%) decreased by 12 kJ/mol, but the decrease in DeltaG(Ca2+SR) was 16 kJ/mol, greater than would be predicted by the fall in DeltaG(%%%ATP%%%) and consistent with increased SR Casup 2sup + release and increased SR Casup 2sup + cycling. Because ischemic preconditioning is reported to decrease SR Casup 2sup + cycling during a subsequent sustained period of ischemia, we examined whether ischemic preconditioning affects the relationship between
the fall in DeltaG(%%%ATP%%%) and the fall in DeltaG(Ca2+SR) during ischemia. We found that preconditioning attenuated the fall in DeltaG(Ca2+SR) during ischemia; the fall in DeltaG(Ca2+SR) was of comparable magnitude to the fall in DeltaG(%%%ATP%%%), and this was associated with a significant improvement in functional recovery during reperfusion. The data suggest that there is both thermodynamic regulation of the SR Casup 2sup + gradient by DeltaG(%%%ATP%%%) and kinetic regulation, which can alter the relationship between DeltaG(%%%ATP%%%) and
DeltaG(Ca2+SR).

8/7/6 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

06704041 EMBASE No: 1996368990
Compensatory mechanisms associated with the hyperdynamic function of %%%phospholamban%%%-deficient mouse hearts
Chu G.; Luo W.; Slack J.P.; Tilgmann C.; Sweet W.E.; Spindler M.; Saupe K.W.; Boivin G.P.; Moravec C.S.; Matlib M.A.; Grupp I.L.; Ingwall J.S.; Kranias E.G.
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Circulation Research (CIRC. RES.) (United States) 1996, 79/6 (1064-1076)
CODEN: CIRUA ISSN: 0009-7330
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

%%%Phospholamban%%% ablation is associated with significant increases in
the sarcoplasmic reticulum Casup 2sup +-ATPase activity and the basal cardiac %%%contractile%%% parameters. To determine whether the observed
phenotype is due to loss of %%%phospholamban%%% alone or to accompanying
compensatory mechanisms, hearts from %%%phospholamban%%%-deficient and
age-matched wild-type mice were characterized in parallel. There were no morphological alterations detected at the light microscope level. Assessment of the protein levels of the cardiac sarcoplasmic reticulum Casup 2sup +-ATPase, calsequestrin, myosin, actin, troponin I, and troponin T revealed no significant differences between %%%phospholamban%%%-deficient
and wild-type hearts. However, the ryanodine receptor protein levels were significantly decreased (25%) upon ablation of %%%phospholamban%%%, probably in an attempt to regulate the release of Casup 2sup + from the sarcoplasmic reticulum, which had a significantly higher diastolic Casup 2sup + content in %%%phospholamban%%%-deficient compared with wild-type
hearts (16.0+/-2.2 versus 8.6+/-1.0 mmol Casup 2sup +/kg dry wt, respectively). The increases in Casup 2sup + content were specific to junctional sarcoplasmic reticulum stores, as there were no alterations in the Casup 2sup + content of the mitochondria or A band. Assessment of %%%ATP%%% levels revealed no alterations, although oxygen consumption increased (1.6-fold) to meet the increased %%%ATP%%% utilization in the hyperdynamic %%%phospholamban%%%-deficient hearts. The increases in

oxygen
consumption were associated with increases (2.2-fold) in the active fraction of the mitochondrial pyruvate dehydrogenase, suggesting increased tricarboxylic acid cycle turnover and %%%ATP%%% synthesis. sup 3sup 1P nuclear magnetic resonance studies demonstrated decreases in phosphocreatine levels and increases in ADP and AMP levels in %%%phospholamban%%%-deficient compared with wild-type hearts. However, the
creatine kinase activity and the creatine kinase reaction velocity were not different between %%%phospholamban%%%-deficient and wild-type hearts. These
findings indicate that ablation of %%%phospholamban%%% is associated with
downregulation of the ryanodine receptor to compensate for the increased Casup 2sup + content in the sarcoplasmic reticulum store and metabolic adaptations to establish a new energetic steady state to meet the increased %%%ATP%%% demand in the hyperdynamic
%%%phospholamban%%%-deficient hearts.

8/7/7 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

06535222 EMBASE No: 1996192659
Purified, reconstituted cardiac Casup 2sup +-ATPase is regulated by %%%phospholamban%%% but not by direct phosphorylation with Casup 2sup +/calmodulin- dependent protein kinase
Reddy L.G.; Jones L.R.; Pace R.C.; Stokes D.L.
Skirball Inst. for Biomolecular Med., New York University Medical Center,New York, NY 10016 United States
Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1996 , 271/25 (14964-14970)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Regulation of %%%calcium%%% transport by sarcoplasmic reticulum provides
increased cardiac %%%contractility%%% in response to beta-adrenergic stimulation. This is due to phosphorylation of %%%phospholamban%%% by cAMP-dependent protein kinase or by
%%%calcium%%%/calmodulin-dependent
protein kinase, which activates the %%%calcium%%% pump (Casup 2sup +-ATPase). Recently, direct phosphorylation of Casup 2sup +- ATPase by %%%calcium%%%/calmodulin-dependent protein kinase has been proposed to provide additional regulation. To investigate these effects in detail, we have purified Casup 2sup +-ATPase from cardiac sarcoplasmic reticulum using
affinity chromatography and reconstituted it with purified, recombinant %%%phospholamban%%%. The resulting proteoliposomes had high rates of %%%calcium%%% transport, which was tightly coupled to %%%ATP%%% hydrolysis
(~1.7 %%%calcium%%% ions transported per %%%ATP%%% molecule hydrolyzed).
Co-reconstitution with %%%phospholamban%%% suppressed both %%%calcium%%%
uptake and ATPase activities by ~50%, and this suppression was fully relieved by a %%%phospholamban%%% monoclonal antibody or by phosphorylation
either with cAMP-dependent protein kinase or with %%%calcium%%% /calmodulin-dependent protein kinase. These effects were consistent with a change in the apparent %%%calcium%%% affinity of Casup 2sup +-ATPase and
not with a change in V(max). Neither the purified, reconstituted cardiac Casup 2sup +-ATPase nor the Casup 2sup +-ATPase in longitudinal cardiac sarcoplasmic reticulum vesicles was a substrate for %%%calcium%%% /calmodulin-dependent protein kinase, and accordingly, we found no effect of %%%calcium%%%/calmodulin-dependent protein kinase phosphorylation on
V(max) for %%%calcium%%% transport.

8/7/8 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

06320543 EMBASE No: 1995357494
Unchanged protein levels of SERCA II and %%%phospholamban%%% but reduced
Casup 2sup + uptake and Casup 2sup +-ATPase activity of cardiac sarcoplasmic reticulum from dilated cardiomyopathy patients compared with patients with nonfailing hearts
Schwinger R.H.G.; Bohm M.; Schmidt U.; Karczewski P.; Bavendick U.; Flesch M.; Krause E.-G.; Erdmann E.
Medizinische Klinik III, Universitat zu Koln, Joseph-Stelzmannstr 9,D-50924 Koln Germany
Circulation (CIRCULATION) (United States) 1995, 92/11 (3220-3228)
CODEN: CIRCA ISSN: 0009-7322
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Background: The aim of the present study was to investigate whether Casup
2sup + uptake into the sarcoplasmic reticulum (SR) is altered in failing human myocardium resulting from dilated cardiomyopathy. Methods and Results: Casup 2sup +-ATPase (SERCA II) activity and Casup 2sup +-dependent
sup 4sup 5Casup 2sup + uptake (oxalate supported, steady state) in isolated vesicles from the SR (VSR) and in crude membrane preparations (CSR) (free Casup 2sup +, 0.01 to 100 mumol/L) from nonfailing (donor hearts, n=13) and terminally failing (%%%heart%%% transplants, dilated cardiomyopathy, n=17)
human myocardium were studied. In the same hearts, protein levels (Western
blot analysis) and mRNA levels (Northern blot analysis) of SERCA II and %%%phospholamban%%% were measured. Increasing concentrations of Casup 2sup
+ were followed by an increased Casup 2sup +-ATPase activity and Casup 2sup
+ uptake, Casup 2sup + uptake activity and Casup 2sup +-ATPase activity in CSR preparations from failing myocardium were significantly reduced compared with nonfailing hearts (Casup 2sup +-ATPase, 163+/-8 and 125+/-7 nmol %%%ATP%%%/mg protein per minute for nonfailing tissue and failing tissue in New York %%%Heart%%% Association (NYHA) class IV, respectively;
Casup 2sup + uptake, 7.1+/-0.8 and 3.5+/-0.3 nmol/mg protein per minute in CSR from nonfailing and NYHA class IV hearts, respectively; P<.05). In contrast, no significant difference was measured in VSR. In the same preparations (CSR and VSR), both SERCA II and %%%phospholamban%%% levels
(Western blot technique with monoclonal antibodies) were unchanged in failing compared with nonfailing tissue, mRNA expression relative GAPDH mRNA for SERCA IIa and for %%%phospholamban%%% was significantly reduced in
failing human myocardium (P<.05). Conclusions: These findings provide evidence that in failing human myocardium caused by dilated cardiomyopathy,
protein levels of SERCA II and %%%phospholamban%%% are unchanged even
though mRNA levels for SERCA II and %%%phospholamban%%% and the SERCA II
function are reduced compared with nonfailing myocardium.

8/7/9 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

05917374 EMBASE No: 1994324248
Energetic modulation of cardiac inotropism and sarcoplasmic reticular Casup 2sup + uptake
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Biochimica et Biophysica Acta - Molecular Cell Research (BIOCHIM. BIOPHYS. ACTA MOL. CELL RES.) (Netherlands) 1994, 1224/1 (22-32)
CODEN: BAMRD ISSN: 0167-4889
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Myocardial %%%contractile%%% performance is a function of sarcoplasmic

reticular Casup 2sup + uptake and release. Casup 2sup + handling is %%%ATP%%%-dependent and can account for up to 40% of total myocardial energy expenditure. We tested the hypothesis that the thermodynamics of the
cytosolic adenylate system can modulate sarcoplasmic reticular Casup 2sup + handling and hence function in intact %%%heart%%%. Cellular energy level was experimentally manipulated by perfusing isolated working guinea-pig hearts with substrate-free medium or media fortified with lactate and/or pyruvate as the main energy substrate. Left ventricular %%%contractile%%%
function was judged by stroke work and intraventricular dP/dt(max). Cytosolic energy level was indexed by measured creatine kinase reactants. Relative to 5 mM lactate, 5 mM pyruvate increased left ventricular stroke work, dP/dt(max) and dP/dt(min), while lowering left ventricular end-diastolic pressure at physiological left atrial and aortic pressures. Pyruvate also doubled cytosolic phosphorylation potentials and increased (%%%ATP%%%)/(ADP) ratio; this energetic enhancement distinguishes pyruvate
from inotropic stimulation by catecholamines, which are known to decrease cytosolic energy level in perfused %%%heart%%%. Sarcoplasmic reticular Casup 2sup + handling was assessed in hearts prelabeled with sup 4sup 5Ca, subjected to sup 4sup 5Ca washout in the presence of different cytosolic energy levels, then stimulated with 10 mM caffeine to release residual sarcoplasmic reticular sup 4sup 5Ca. When ryanodine (1 muM) was applied to open Casup 2sup + channels and thereby released sup 4sup 5Ca from the sarcoplasmic reticulum during washout, caffeine-stimulated sup 4sup 5Ca release was decreased 96%, demonstrating that virtually the entire caffeine-sensitive sup 4sup 5Ca pool was located in the sarcoplasmic reticulum. In detailed comparisons of pyruvate-energized vs. substrate-free deenergized hearts, an inverse relationship between cytosolic energy level and caffeine-mobilized sup 4sup 5Ca pool size was observed. Thus, caffeine-induced sup 4sup 5Ca release was decreased 60% by pyruvate energization and increased 2.5-fold by substrate-free deenergization. Taken together, these results support the hypothesis that enhancement of myocardial inotropism by energy-yielding substrate is mediated by increased sarcoplasmic reticular Casup 2sup + loading/release. Thus we propose that the known control of sarcoplasmic reticular Casup 2sup + turnover by the protein kinase/%%%phospholamban%%% system can be modulated by cytosolic
energy level.

8/7/10 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE
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05834365 EMBASE No: 1994249457
Casup 2sup +-transporting ATPase, %%%phospholamban%%%, and calsequestrin
levels in nonfailing and failing human myocardium
Movsesian M.A.; Karimi M.; Green K.; Jones L.R.
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Circulation (CIRCULATION) (United States) 1994, 90/2 (653-657)
CODEN: CIRCA ISSN: 0009-7322
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Background: Observations of abnormalities in the diastolic components of intracellular Casup 2sup + transients in failing human left ventricular myocardium have raised the possibility that reductions in the level or function of sarcoplasmic reticulum proteins involved in Casup 2sup + transport contribute to the pathophysiology of dilated cardiomyopathy in humans. Functional assays, however, have revealed no differences in %%%ATP%%%-dependent Casup 2sup + transport or its modulation by %%%phospholamban%%% in sarcoplasmic reticulum-enriched microsomes prepared
from nonfailing and failing human left ventricular myocardium. The purpose of the present study was to quantify protein levels of Casup 2sup +-transporting ATPase, %%%phospholamban%%%, and calsequestrin directly in nonfailing and failing human left ventricular myocardium. Methods and Results: Total protein extracts were prepared from nonfailing left ventricular myocardium from the hearts of unmatched organ donors with normal left ventricular %%%contractility%%% (n=6) and from failing left ventricular myocardium from the excised hearts of transplant recipients with class IV %%%heart%%% %%%failure%%% resulting from idiopathic dilated
cardiomyopathy (n=6). Casup 2sup +-transporting ATPase, %%%phospholamban%%%
, and calsequestrin contents were determined by quantitative immunoblotting with monoclonal and affinity-purified polyclonal antibodies. The levels of the three proteins were identical in nonfailing and failing human left ventricular myocardium. Conclusions: These results indicate that protein levels of Casup 2sup +-transporting ATPase, %%%phospholamban%%%, and calsequestrin are not diminished in failing human left ventricular myocardium and that downregulation of the Casup 2sup +-transporting ATPase
and %%%phospholamban%%% is not part of the molecular pathophysiology of
dilated cardiomyopathy in humans.

8/7/11 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE
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05570985 EMBASE No: 1993339085
Left ventricular diastolic function in the normal and %%%diseased%%% %%%heart%%%: Perspectives for the anesthesiologist (second of two parts)
Pagel P.S.; Grossman W.; Haering J.M.; Warltier D.C.
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Anesthesiology (ANESTHESIOLOGY) (United States) 1993, 79/5 (1104-1120)
CODEN: ANESA ISSN: 0003-3022
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Several important questions remain to be answered by future research. First, it is unclear whether any abnormal index of diastolic function can be used to estimate %%%disease%%% severity, or to prognostically identify patients who will subsequently develop systolic abnormalities or frank left ventricular dysfunction. A temporal relationship between the appearance of diastolic dysfunction and ultimate left ventricular decompensation may, theoretically, exist, but such a relationship has yet to be established. Second, a growing body of evidence indicates that pharmacologic therapy with Casup 2sup + channel antagonists, beta-adrenergic agonists or antagonists, phosphodiesterase inhibitors, or angiotensin converting enzyme inhibitors may acutely or chronically benefit certain patients with diastolic dysfunction. Whether the impact of early recognition and therapeutic intervention in patients with diastolic dysfunction can be translated into an improvement of quality of life or enhanced survival remains unknown. Third, recent evidence indicates that fundamental changes in the biochemistry of the cardiac myocyte may represent a final common pathway for the development of congestive %%%heart%%%
%%%failure%%%
resulting from intrinsic cardiac %%%disease%%%. Altered expression of genes
coding for the %%%ATP%%%-dependent Casup 2sup + pumps in the sarcolemma and
the sarcoplasmic reticulum, regulatory proteins such as %%%phospholamban%%%
, and the proteins composing the %%%contractile%%% apparatus have been identified that play critical roles in the pathophysiology of myocardial %%%failure%%%, and have important implications for potential pharmacologic
therapy. Future research will more clearly elucidate these cellular and biochemical mechanisms of left ventricular %%%failure%%%. Lastly, although
intravenous and inhalational anesthetics produce derangements in normal diastolic function to varying degrees, whether the effects of these agents on diastolic performance are exacerbated in %%%disease%%% processes manifested by abnormal diastolic mechanics requires further evaluation.

8/7/12 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE
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05348072 EMBASE No: 1993116157
Increased activity of the sarcoplasmic reticular %%%calcium%%% pump in

porcine stunned myocardium
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Cardiovascular Research (CARDIOVASC. RES.) (United Kingdom) 1993, 27/3
(520-524)
CODEN: CVREA ISSN: 0008-6363
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Objective: The aim was to determine whether changes in sarcoplasmic reticular Casup 2sup + transport activity and the degree of phosphorylation of %%%phospholamban%%% of 'stunned' myocardium are involved in the reversible depression of %%%contractile%%% function. Methods: In anaesthetised open chest swine, stunning was induced by subjecting the myocardium perfused by the left anterior descending coronary artery to two cycles of 10 min of occlusion and 30 min of reperfusion. Before and after stunning, systemic haemodynamic variables and regional myocardial function and perfusion were determined, while biopsies were taken for determination of the content of high energy phosphate compounds. Sarcoplasmic reticular function (%%%ATP%%% dependent Casup 2sup + transport and phosphorylation of
%%%phospholamban%%%) of the stunned and control myocardium was determined
at the end of the stunning protocol. Results: In the stunned myocardium the segment length shortening decreased from 17.4(SD 4.0)% to 3.5(4.4)%, while
perfusion was 38% less than at baseline. %%%ATP%%% and total adenine nucleotide levels of the stunned myocardium were about 35% lower than in the control myocardium, but the energy charge was normal as creatine phosphate levels had increased by 66% over the content determined at baseline. Casup 2sup + uptake by the sarcoplasmic reticulum isolated from the stunned region was 17% (p<0.05) higher than Casup 2sup + uptake from the control region (1240(303) and 1450(280) nmol - minsup -sup 1 - mgsup -sup 1 protein, respectively). In the presence of exogenous cyclic AMP dependent protein kinase the amount of sup 3sup 2P incorporated into %%%phospholamban%%% was similar for both myocardial regions. Conclusions:
In this model of stunned porcine myocardium, the phosphorylation state of %%%phospholamban%%% was unchanged, but Casup 2sup + uptake by the sarcoplasmic reticulum was slightly increased. The results indicate that a change in active Casup 2sup + transport by the sarcoplasmic reticulum is most likely not to be the principal cause of %%%contractile%%% dysfunction
of stunned myocardium.

8/7/13 (Item 1 from file: 144)
DIALOG(R)File 144:Pascal

13820298 PASCAL No.: 98-0536492
Regulation of the Ca SUP 2 SUP + gradient across the sarcoplasmic reticulum in perfused rabbit %%%heart%%%: A SUP 1 SUP 9 F nuclear magnetic
resonance study
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Journal: Circulation research, %%%1998%%%, 83 (9) 898-907
ISSN: 0009-7330 CODEN: CIRUAL Availability: INIST-7216; 354000070695790030
No. of Refs.: 44 ref.
Document Type: P (Serial) ; A (Analytic)
Country of Publication: United States
Language: English
Myocardial %%%contractility%%% depends on Ca SUP 2 SUP + release from and
uptake into the sarcoplasmic reticulum (SR). The Ca SUP 2 SUP + gradient between the SR matrix and the cytosol (SR Ca SUP 2 SUP + gradient) is maintained by the SR Ca SUP 2 SUP + -ATPase using the free energy available
from hydrolysis of %%%ATP%%%. The activity of the SR Ca SUP 2 SUP + -ATPase
is not only dependent on the energy state of the cell but is also kinetically regulated by SR proteins such as %%%phospholamban%%%. To
evaluate the importance of thermodynamic and kinetic regulation of the SR Ca SUP 2 SUP + gradient, we examined the relationship between the energy
available from %%%ATP%%% hydrolysis (DELTA G SUB A SUB T SUB P) and the
energy required for maintenance of the SR Ca SUP 2 SUP + gradient (DELTA G
SUB C SUB a 2+ SUB S SUB R) during physiological and pathological manipulations that alter DELTA G SUB A SUB T SUB P and the phosphorylation
state of %%%phospholamban%%%. We used our previously developed SUP 1 SUP 9
F nuclear magnetic resonance method to measure the ionized (Ca SUP 2 SUP +
) in the SR of Langendorff-perfused rabbit hearts. We found that addition of either pyruvate or isoproterenol resulted in an increase in left ventricular developed pressure and an increase in (Ca SUP 2 SUP +) SUB S SUB R , Pyruvate increased DELTA G SUB A SUB T SUB P , and the increase in
the SR Ca SUP 2 SUP + gradient was matched to the increase in DELTA G SUB A
SUB T SUB P ; DELTA G SUB A SUB T SUB P increased from 58.3 +- 0.5 to 60.4
+- 1.0 kJ/mol (P<0.05), and DELTA G SUB C SUB a 2+ SUB S SUB R increased
from 47.1 +- 0.3 to 48.5 +- 0.1 kJ/mol (P<0.05). In contrast, the increase in the SR Ca SUP 2 SUP + gradient in the presence of isoproterenol occurred despite a decline in DELTA G SUB A SUB T SUB P from 58.3 +- 0.5 to 55.8 +-
0.6 kJ/mol. Thus, the data indicate that the SR Ca SUP 2 SUP + gradient can
be increased by an increase in DELTA G SUB A SUB T SUB P , and that the
positive inotropic effect of pyruvate can be explained by improved energy-linked SR Ca SUP 2 SUP + handling, whereas the results with isoproterenol are consistent with removal of the kinetic limitation of %%%phospholamban%%% on the activity of the sarcoplasmic/endoplasmic
reticulum Ca SUP 2 SUP + -ATPase, which allows the SR Ca SUP 2 SUP + gradient to move closer to its thermodynamic limit. Ischemia decreases DELTA G SUB A SUB T SUB P , and this should also have an effect on SR Ca
SUP 2 SUP + handling. During 30 minutes of ischemia, DELTA G SUB A SUB T
SUB P decreased by 12 kJ/mol, but the decrease in DELTA G SUB C SUB a 2+
SUB S SUB R was 16 kJ/mol, greater than would be predicted by the fall in
DELTA G SUB A SUB T SUB P and consistent with increased SR Ca SUP 2 SUP +
release and increased SR Ca SUP 2 SUP + cycling. Because ischemic preconditioning is reported to decrease SR Ca SUP 2 SUP + cycling during a subsequent sustained period of ischemia, we examined whether ischemic preconditioning affects the relationship between the fall in DELTA G SUB A
SUB T SUB P and the fall in DELTA G SUB C SUB a 2+ SUB S SUB R during
ischemia. We found that preconditioning attenuated the fall in DELTA G SUB
C SUB a 2+SR during ischemia; the fall in DELTA G SUB C SUB a 2+SR was of
comparable magnitude to the fall in DELTA G SUB A SUB T SUB P , and this
was associated with a significant improvement in functional recovery during reperfusion. The data suggest that there is both thermodynamic regulation of the SR Ca SUP 2 SUP + gradient by DELTA G SUB A SUB T SUB P and kinetic
regulation, which can alter the relationship between DELTA G SUB A SUB T
SUB P and DELTA G SUB C SUB a 2+ SUB S SUB R .

8/7/14 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

02978104 79154525 PMID: 34741
Myocardial metabolism and %%%heart%%% %%%disease%%%.
Opie L H
Japanese circulation journal (JAPAN) Nov %%%1978%%%, 42 (11) p1223-47, ISSN 0047-1828 Journal Code: 7806868
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Anoxia has been compared with ischaemia. The abrupt restoration of either oxygen of flow may accelerate cardiac damage. Anoxic stimulation of glycolysis (Pasteur effect) is inhibited during ischaemia by lactate and proton accumulation at the levels of phosphofructokinase and glyceraldehyde-3-phosphate dehydrogenase. Anaerobic glycolysis provides lactate and %%%ATP%%% ; breakdown of the latter provides protons. During
partial respiration thought to occur in partial ischaemia, continued production of CO2 is a factor contributing to intracellular acidosis; mitochondrial %%%ATP%%% when formed by continued respiration also yields
protons when ultimately broken down. The endoproducts of aerobic glycolysis (pyruvate and NADH) are transported into the mitochondria by the malate-aspartate cycle and by pyruvate dehydrogenase activity. Adenine nucleotide transferase activity normally transfers the mitochondrially-made %%%ATP%%% to the cytoplasm, but acyl CoA accumulates in ischaemia (or
during perfusions with high circulating free fatty acids) to inhibit the transferase. The mitochondrial creatine kinase is thought to transform %%%ATP%%% transported outwards into creatine phosphate which can permeate
the outer mitochondrial membrane. Further compartmentation of %%%ATP%%% may
be by other creatine kinase isoenzymes or in relation to the cell membrane. The glycogenolytic-sarcoplasmic reticulum complex links a glycogen pool to the sarcoplasmic reticulum. Cyclic AMP may regulate admission of %%%calcium%%% to the cell during the plateau of the action potential and promote %%%calcium%%% uptake by the sarcoplasmic reticulum by phosphorylation of %%%phospholamban%%%. The latter promotes the activity of
the %%%calcium%%%-transport ATPase. %%%Calcium%%% and cyclic AMP may also
interact at the level of the %%%contractile%%% proteins where cyclic AMP
phosphrylates troponin. Cyclic GMP generally has opposite effects to cyclic AMP and undergoes opposite changes in the frog cardiac cycle to those of cyclic AMP. A present it is reasonable to suppose that physiological effects of adrenaline or of cholinergic agents on the myocardium are mediated by cyclic AMP or cyclic GMP, respectively, but this hypothesis still lacks firm support. There is an association between tissue cyclic AMP and ventricular fibrillation after coronary ligation, and direct evidence for a role of cyclic AMP in promoting arrhythmias has been obtained by studies on the ventricular fibrillation threshold in the rat %%%heart%%%. However, there are other mechanisms, involving first the effects of substrates on the action potential duration, and secondly, the fast channel, which can also give rise to the development of malignant arrhythmias. (168 Refs.)
Record Date Created: 19790629
Record Date Completed: 19790629
? s phospholamban and (administ? or treat? or inject?)
Processing
Processed 10 of 22 files ...
Processing
Processing
Processed 20 of 22 files ...
Completed processing all files
6858 PHOSPHOLAMBAN
5093868 ADMINIST?
11837445 TREAT?
2328761 INJECT?
S9 873 PHOSPHOLAMBAN AND (ADMINIST? OR TREAT? OR INJECT?)
? s s9 and PY<2000
Processing
Processing
Processed 10 of 22 files ...
Processing
Processing
Processed 20 of 22 files ...
Processing
Completed processing all files
873 S9
100969173 PY<2000
S10 549 S9 AND PY<2000
? s s10 and (heart or cardiac)
549 S10
2864830 HEART
1242925 CARDIAC
S11 512 S10 AND (HEART OR CARDIAC)
? t s11/7/1-5
>>>Format 7 is not valid in file 143

11/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12536375 BIOSIS NO.: 200000289877
Method for the prevention and %%%treatment%%% of stunned myocardium.
AUTHOR: Haikala Heimo(a); Kaheinen Petri; Levijoki Jouko; Kaivola Juh; Ovaska Martti; Pystynen Jarmo
AUTHOR ADDRESS: (a)Espoo**Finland
JOURNAL: Official Gazette of the United States Patent and Trademark Office
Patents 1227 (3):pNo pagination Oct. 19, %%%1999%%%
MEDIUM: e-file.
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A method for the prevention and %%%treatment%%% of stunning of
the %%%heart%%% subsequent to ischemia-reperfusion is described. The method comprises %%%administering%%% a therapeutically effective amount
of a %%%phospholamban%%% inhibitor to a patient.
%%%Phospholamban%%%
inhibitors relieve the inhibitory effect of %%%phospholamban%%% on %%%cardiac%%% sarcoplasmic reticulum Ca2+ -ATPase.

11/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12258730 BIOSIS NO.: 200000012232
Elevated levels of endogenous adenosine alter metabolism and enhance reduction in contractile function during low-flow ischemia: Associated changes in expression of Ca2+-ATPase and %%%phospholamban%%%.
AUTHOR: Sommerschild Hilchen T(a); Lunde Per Kristian; Deindl Elisabeth; Jynge Per; Ilebekk Arnfinn; Kirkeboen Knut Arvid
AUTHOR ADDRESS: (a)Institute for Experimental Medical Research, Ulleval
Hospital, N-0407, Oslo**Norway
JOURNAL: Journal of Molecular and Cellular Cardiology 31 (10):p1897-1911 Oct., %%%1999%%%
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Adenosine has several potentially cardioprotective effects including vasodilatation, reduction in %%%heart%%% rate and alterations in metabolism. Adenosine inhibits catecholamine-induced increase in contractile function mainly through inhibition of phosphorylation of

%%%phospholamban%%% (PLB), the main regulatory protein of Ca2+-ATPase in
sarcoplasmic reticulum (SR), and during ischemia it reduces calcium (Ca2+) overload. In this study we examined the effects of endogenous adenosine on contractile function and metabolism during low-flow ischemia (LFI) and investigated whether endogenous adenosine can alter expression of the Ca2+-ATPase/PLB-system and other Ca2+-regulatory proteins. Isolated blood-perfused piglet hearts underwent 120 min 10% flow. Hearts were %%%treated%%% with either saline, the adenosine receptor blocker (8)-sulfophenyl theophylline (8SPT, 300 mumol/l) or the nucleoside transport inhibitor draflazine (1 mumol/l). During LFI, 8SPT did not substantially influence metabolic or fun ctional responses. However, draflazine enhanced the reduction in %%%heart%%% rate, contractile force
and MVO2, with less release of H+ and CO2. Before LFI there were no significant differences between groups for any of the proteins (Ca2+-ATPase, ryanodine-receptor, Na+/K+-ATPase) or mRNAs (Ca2+-ATPase,
PLB, calsequestrin, Na+/Ca2+-exchanger) measured. At end of LFI mRNA-level of PLB was higher in draflazine-%%%treated%%% hearts compared
to both other groups (P<0.01 vs both). Also, at end of LFI protein-level of Ca2+-ATPase was lower in draflazine-%%%treated%%% hearts (P<0.05 vs
both), and a parallel trend towards a lower mRNA-level was seen (P=0.11 vs saline and P=0.43 vs 8SPT). During LFI tissue Ca2+ tended to rise in saline- and 8SPT-%%%treated%%% hearts but not in draflazine-%%%treated%%%
hearts (at end of LFI, P = 0.01 vs 8SPT). We conclude that the amount of adenosine normally produced during LFI does not substantially influence function and metabolism. However, increased endogenous levels by draflazine enhance downregulation of function and reduce signs of anaerobic metabolism. At end of LFI associated changes in expression of PLB and Ca2+-ATPase were seen. The functional significance was not determined in the present study. However, altered protein-levels might influence Ca2+-handling in sarcoplasmic reticulum and thus affect contractile force and tolerance to ischemia.

11/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12199975 BIOSIS NO.: 199900494824
Status of Ca2+/calmodulin protein kinase phosphorylation of %%%cardiac%%%
SR proteins in ischemia-reperfusion.
AUTHOR: Netticadan Thomas; Temsah Rana; Osada Mitsuru; Dhalla Naranjan S(a)
AUTHOR ADDRESS: (a)Inst. of Cardiovascular Sciences, St. Boniface General
Hospital Research Centre, 351 Tache Ave., Winnipeg, MB, R2H 2A6**Canada
JOURNAL: American Journal of Physiology 277 (3 PART 1):pC384-C391 Sept.,
%%%1999%%%
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Although the sarcoplasmic reticulum (SR) is known to regulate the
intracellular concentration of Ca2+ and the SR function has been shown to become abnormal during ischemia-reperfusion in the %%%heart%%%, the mechanisms for this defect are not fully understood. Because phosphorylation of SR proteins plays a crucial role in the regulation of SR function, we investigated the status of endogenous Ca2+/calmodulin-dependent protein kinase (CaMK) and exogenous cAMP-dependent protein kinase (PKA) phosphorylation of the SR proteins in
control, ischemic (I), and ischemia-reperfused (I/R) hearts %%%treated%%%
or not %%%treated%%% with superoxide dismutase (SOD) plus catalase (CAT). SR and cytosolic fractions were isolated from control, I, and I/R hearts %%%treated%%% or not %%%treated%%% with SOD plus CAT, and the SR protein
phosphorylation by CaMK and PKA, the CaMK- and PKA-stimulated Ca2+ uptake, and the CaMK, PKA, and phosphatase activities were studied. The SR CaMK and CaMK-stimulated Ca2+ uptake activities, as well as CaMK phosphorylation of Ca2+ pump ATPase (SERCA2a) and %%%phospholamban%%%
(PLB), were significantly decreased in both I and I/R hearts. The PKA phosphorylation of PLB and PKA-stimulated Ca2+ uptake were reduced significantly in the I/R hearts only. Cytosolic CaMK and PKA activities were unaltered, whereas SR phosphatase activity in the I and I/R hearts was depressed. SOD plus CAT %%%treatment%%% prevented the observed
alterations in SR CaMK and phosphatase activities, CaMK and PKA phosphorylations, and CaMK- and PKA-stimulated Ca2+ uptake. These results
indicate that depressed CaMK phosphorylation and CaMK-stimulated Ca2+ uptake in I/R hearts may be due to a depression in the SR CaMK activity. Furthermore, prevention of the I/R-induced alterations in SR protein phosphorylation by SOD plus CAT %%%treatment%%% is consistent with the
role of oxidative stress during ischemia-reperfusion injury in the %%%heart%%%.

11/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12199676 BIOSIS NO.: 199900494525
Calcium regulatory proteins and their alteration by transgenic approaches.
AUTHOR: Dillmann W H(a)
AUTHOR ADDRESS: (a)Endocrinology and Metabolism, University of California
San Diego, 9500 Gilman Drive (BSB 1 5063), La Jolla, CA, 92093-0618**USA
JOURNAL: American Journal of Cardiology 83 (12A):p89H-91H June 17, %%%1999%%%
ISSN: 0002-9149
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Abnormalities in calcium flux have been linked to abnormal contractile behavior of the %%%heart%%% in patients with congestive %%%heart%%% failure as well as in animal models. Decreased activity or levels of the calcium adenosine triphosphatase of the sarco(endo)plasmic reticulum (SERCA2) particularly have been known to cause a delay in calcium transients. The SERCA2 protein pumps 2 moles of calcium per mole of adenosine triphosphate (ATP) split from the cytoplasm into the sarcoplasmic reticulum, thus lowering the free cytoplasmic calcium concentration. It therefore is of interest to identify mechanisms by which SERCA activity could be increased in the %%%heart%%%. To determine
influences of increased expression of the SERCA2 gene on calcium transient and contractile behavior, we constructed transgenic mice and rats expressing a SERCA2 transgene in their %%%heart%%%. In these animals, a 20% increase in SERCA levels occurs due to additional expression of the SERCA transgene. This leads to a corresponding increase in contractile activity as determined by the increase in left ventricular pressure measured as dP/dtmax and decrease in diastolic ventricular pressure determined as dP/dtmin. Similarly, isolated %%%cardiac%%% myocytes obtained from the %%%heart%%% of transgenic mice showed an accelerated calcium transient and increased speed of shortening and relengthening as determined by edge detection. To determine if SERCA2 transgene expression could have a compensatory effect on the contractile behavior of the %%%heart%%% in transgenic mice expressing SERCA2, these
mice were made hypothyroid, and papillary muscle function was determined. Contractile behavior of the papillary muscle of wild-type hypothyroid mice showed a significant increase in muscle relaxation time (RT50). In contrast, SERCA2 transgenic hypothyroid mice showed normal contractile behavior of papillary muscle. A compensatory effect of SERCA transgene expression was therefore demonstrated. In addition, we constructed

transgenic rats expressing a SERCA2 transgene in which constriction of the ascending aorta induced %%%cardiac%%% hypertrophy and a delayed contraction of papillary muscle. In preliminary results, we found that SERCA2 transgenic rats submitted to ascending aortic constriction did not show the delayed relaxation of papillary muscle as was found in wild-type rats submitted to aortic constriction. In addition, adenoviral vectors expressing transgenes for calcium-handling proteins can be used to improve %%%cardiac%%% myocyte contraction. Adenoviruses expressing a SERCA transgene or a mutant %%%phospholamban%%% transgene exhibiting dominant negative action were used to infect isolated myocytes %%%treated%%% with a phorbol ester (phorbol 12-myristate 13-acetate), which delays the calcium transients. The calcium transients and contractile behavior of the isolated myocytes indicated that increased SERCA expression or increased expression of mutant %%%phospholamban%%% transgene led to increased SERCA2 activity, resulting in an increased contractile phenotype. Recent findings by other investigators also indicate that decreased SERCA2 activity can be increased under in vivo conditions using adenoviral vector-based SERCA2 expression. A gene therapy type of approach delivering increased amounts of SERCA or %%%phospholamban%%% mutants leading to increased SERCA activity should therefore be considered in the future.

11/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12173890 BIOSIS NO.: 199900468739
Gi protein-mediated functional compartmentalization of %%%cardiac%%% beta2-adrenergic signaling.
AUTHOR: Kuschel Meike; Zhou Ying-Ying; Cheng Heping; Zhang Sheng-Jun; Chen Ye; Lakatta Edward G; Xiao Rui-Ping(a)
AUTHOR ADDRESS: (a)Laboratory of Cardiovascular Science, Gerontology Research Center, NIA, National Institutes of Health, 5600 Nathan Shock Dr., Baltimore, MD, 21224**USA
JOURNAL: Journal of Biological Chemistry 274 (31):p22048-22052 July 30, %%%1999%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In contrast to beta1-adrenoreceptor (beta1-AR) signaling, beta2-AR stimulation in cardiomyocytes augments L-type Ca2+ current in a cAMP-dependent protein kinase (PKA)-dependent manner but fails to phosphorylate %%%phospholamban%%%, indicating that the beta2-AR-induced cAMP/PKA signaling is highly localized. Here we show that inhibition of Gi proteins with pertussis toxin (PTX) permits a full %%%phospholamban%%% phosphorylation and a de novo relaxant effect following beta2-AR stimulation, converting the localized beta2-AR signaling to a global signaling mode similar to that of beta1-AR. Thus, beta2-AR-mediated Gi activation constricts the cAMP signaling to the sarcolemma. PTX %%%treatment%%% did not significantly affect the beta2-AR-stimulated PKA activation. Similar to Gi inhibition, a protein phosphatase inhibitor, calyculin A (3 X 10-8 M), selectively enhanced the beta2-AR but not beta1-AR-mediated contractile response. Furthermore, PTX and calyculin A %%%treatment%%% had a non-additive potentiating effect on the beta2-AR-mediated positive inotropic response. These results suggest that the interaction of the beta2-AR-coupled Gi and Gs signaling affects the local balance of protein kinase and phosphatase activities. Thus, the additional coupling of beta2-AR to Gi proteins is a key factor causing the compartmentalization of beta2-AR-induced cAMP signaling.

? ds

Set Items Description
S1 1736 HEART AND (DISEAS? OR FAILURE?) AND PHOSPHOLAMBAN
S2 927 RD S1 (unique items)
S3 518 S2 AND PY<2000
S4 72 S3 AND (TREAT? OR AMELORIAT?)
S5 265 S3 AND CONTRACT?
S6 225 S5 NOT S4
S7 172 S6 AND CALCIUM
S8 14 S7 AND ATP
S9 873 PHOSPHOLAMBAN AND (ADMINIST? OR TREAT? OR INJECT?)
S10 549 S9 AND PY<2000
S11 512 S10 AND (HEART OR CARDIAC)
? s s11/de
>>>Term "DE" is not defined in one or more files
S12 336 S11/DE
? t s12/7/1-5
>>>Format 7 is not valid in file 143

12/7/1 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

12536375 BIOSIS NO.: 200000289877
Method for the prevention and treatment of stunned myocardium.
AUTHOR: Haikala Heimo(a); Kaheinen Petri; Levijoki Jouko; Kaivola Juh; Ovaska Martti; Pystynen Jarmo
AUTHOR ADDRESS: (a)Espoo**Finland
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1227 (3):pNo pagination Oct. 19, 1999
MEDIUM: e-file.
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A method for the prevention and treatment of stunning of the heart subsequent to ischemia-reperfusion is described. The method comprises administering a therapeutically effective amount of a phospholamban inhibitor to a patient. Phospholamban inhibitors relieve the inhibitory effect of phospholamban on cardiac sarcoplasmic reticulum Ca2+ -ATPase.

12/7/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2003 BIOSIS. All rts. reserv.

12258730 BIOSIS NO.: 200000012232
Elevated levels of endogenous adenosine alter metabolism and enhance reduction in contractile function during low-flow ischemia: Associated changes in expression of Ca2+-ATPase and phospholamban.
AUTHOR: Sommerschild Hilchen T(a); Lunde Per Kristian; Deindl Elisabeth; Jynge Per; Ilebekk Arnfinn; Kirkeboen Knut Arvid
AUTHOR ADDRESS: (a)Institute for Experimental Medical Research, Ulleval Hospital, N-0407, Oslo**Norway
JOURNAL: Journal of Molecular and Cellular Cardiology 31 (10):p1897-1911 Oct., 1999
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Adenosine has several potentially cardioprotective effects including vasodilatation, reduction in heart rate and alterations in metabolism. Adenosine inhibits catecholamine-induced increase in contractile function mainly through inhibition of phosphorylation of phospholamban (PLB), the main regulatory protein of Ca2+-ATPase in sarcoplasmic reticulum (SR), and during ischemia it reduces calcium (Ca2+) overload. In this study we examined the effects of endogenous adenosine on contractile function and metabolism during low-flow ischemia (LFI) and investigated whether endogenous adenosine can alter expression of the Ca2+-ATPase/PLB-system and other Ca2+-regulatory proteins. Isolated blood-perfused piglet hearts underwent 120 min 10% flow. Hearts were treated with either saline, the adenosine receptor blocker

(8)-sulfophenyl theophylline (8SPT, 300 mumol/l) or the nucleoside transport inhibitor draflazine (1 mumol/l). During LFI, 8SPT did not substantially influence metabolic or fun ctional responses. However, draflazine enhanced the reduction in heart rate, contractile force and MVO2, with less release of H+ and CO2. Before LFI there were no significant differences between groups for any of the proteins (Ca2+-ATPase, ryanodine-receptor, Na+/K+-ATPase) or mRNAs (Ca2+-ATPase,
PLB, calsequestrin, Na+/Ca2+-exchanger) measured. At end of LFI mRNA-level of PLB was higher in draflazine-treated hearts compared to both other groups (P<0.01 vs both). Also, at end of LFI protein-level of Ca2+-ATPase was lower in draflazine-treated hearts (P<0.05 vs both), and a parallel trend towards a lower mRNA-level was seen (P=0.11 vs saline and P=0.43 vs 8SPT). During LFI tissue Ca2+ tended to rise in saline- and 8SPT-treated hearts but not in draflazine-treated hearts (at end of LFI, P = 0.01 vs 8SPT). We conclude that the amount of adenosine normally produced during LFI does not substantially influence function and metabolism. However, increased endogenous levels by draflazine enhance downregulation of function and reduce signs of anaerobic metabolism. At end of LFI associated changes in expression of PLB and Ca2+-ATPase were seen. The functional significance was not determined in the present study. However, altered protein-levels might influence Ca2+-handling in sarcoplasmic reticulum and thus affect contractile force and tolerance to ischemia.

12/7/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12199975 BIOSIS NO.: 199900494824
Status of Ca2+/calmodulin protein kinase phosphorylation of cardiac SR proteins in ischemia-reperfusion.
AUTHOR: Netticadan Thomas; Temsah Rana; Osada Mitsuru; Dhalla Naranjan S(a)
AUTHOR ADDRESS: (a)Inst. of Cardiovascular Sciences, St. Boniface General
Hospital Research Centre, 351 Tache Ave., Winnipeg, MB, R2H 2A6**Canada
JOURNAL: American Journal of Physiology 277 (3 PART 1):pC384-C391 Sept.,
1999
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Although the sarcoplasmic reticulum (SR) is known to regulate the
intracellular concentration of Ca2+ and the SR function has been shown to become abnormal during ischemia-reperfusion in the heart, the mechanisms for this defect are not fully understood. Because phosphorylation of SR proteins plays a crucial role in the regulation of SR function, we investigated the status of endogenous Ca2+/calmodulin-dependent protein kinase (CaMK) and exogenous cAMP-dependent protein kinase (PKA) phosphorylation of the SR proteins in control, ischemic (I), and ischemia-reperfused (I/R) hearts treated or not treated with superoxide dismutase (SOD) plus catalase (CAT). SR and cytosolic fractions were isolated from control, I, and I/R hearts treated or not treated with SOD plus CAT, and the SR protein phosphorylation by CaMK and PKA, the CaMK- and PKA-stimulated Ca2+ uptake, and the CaMK, PKA, and phosphatase activities were studied. The SR CaMK and CaMK-stimulated Ca2+ uptake activities, as well as CaMK phosphorylation of Ca2+ pump ATPase (SERCA2a)
and phospholamban (PLB), were significantly decreased in both I and I/R hearts. The PKA phosphorylation of PLB and PKA-stimulated Ca2+ uptake were reduced significantly in the I/R hearts only. Cytosolic CaMK and PKA activities were unaltered, whereas SR phosphatase activity in the I and I/R hearts was depressed. SOD plus CAT treatment prevented the observed
alterations in SR CaMK and phosphatase activities, CaMK and PKA phosphorylations, and CaMK- and PKA-stimulated Ca2+ uptake. These results
indicate that depressed CaMK phosphorylation and CaMK-stimulated Ca2+ uptake in I/R hearts may be due to a depression in the SR CaMK activity. Furthermore, prevention of the I/R-induced alterations in SR protein phosphorylation by SOD plus CAT treatment is consistent with the role of oxidative stress during ischemia-reperfusion injury in the heart.

12/7/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12199676 BIOSIS NO.: 199900494525
Calcium regulatory proteins and their alteration by transgenic approaches.
AUTHOR: Dillmann W H(a)
AUTHOR ADDRESS: (a)Endocrinology and Metabolism, University of California
San Diego, 9500 Gilman Drive (BSB 1 5063), La Jolla, CA, 92093-0618**USA
JOURNAL: American Journal of Cardiology 83 (12A):p89H-91H June 17, 1999
ISSN: 0002-9149
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Abnormalities in calcium flux have been linked to abnormal contractile behavior of the heart in patients with congestive heart failure as well as in animal models. Decreased activity or levels of the calcium adenosine triphosphatase of the sarco(endo)plasmic reticulum (SERCA2) particularly have been known to cause a delay in calcium transients. The SERCA2 protein pumps 2 moles of calcium per mole of adenosine triphosphate (ATP) split from the cytoplasm into the sarcoplasmic reticulum, thus lowering the free cytoplasmic calcium concentration. It therefore is of interest to identify mechanisms by which SERCA activity could be increased in the heart. To determine influences of increased expression of the SERCA2 gene on calcium transient and contractile behavior, we constructed transgenic mice and rats expressing a SERCA2 transgene in their heart. In these animals, a 20% increase in SERCA levels occurs due to additional expression of the SERCA transgene. This leads to a corresponding increase in contractile activity as determined by the increase in left ventricular pressure measured as dP/dtmax and decrease in diastolic ventricular pressure determined as dP/dtmin. Similarly, isolated cardiac myocytes obtained from the heart of transgenic mice showed an accelerated calcium transient and increased speed of shortening and relengthening as determined by edge detection. To determine if SERCA2 transgene expression could have a compensatory effect on the contractile behavior of the heart in transgenic mice expressing SERCA2, these mice were made hypothyroid, and
papillary muscle function was determined. Contractile behavior of the papillary muscle of wild-type hypothyroid mice showed a significant increase in muscle relaxation time (RT50). In contrast, SERCA2 transgenic hypothyroid mice showed normal contractile behavior of papillary muscle. A compensatory effect of SERCA transgene expression was therefore demonstrated. In addition, we constructed transgenic rats expressing a SERCA2 transgene in which constriction of the ascending aorta induced cardiac hypertrophy and a delayed contraction of papillary muscle. In preliminary results, we found that SERCA2 transgenic rats submitted to ascending aortic constriction did not show the delayed relaxation of papillary muscle as was found in wild-type rats submitted to aortic constriction. In addition, adenoviral vectors expressing transgenes for calcium-handling proteins can be used to improve cardiac myocyte contraction. Adenoviruses expressing a SERCA transgene or a mutant phospholamban transgene exhibiting dominant negative action were used to infect isolated myocytes treated with a phorbol ester (phorbol 12-myristate 13-acetate), which delays the calcium transients. The calcium transients and contractile behavior of the isolated myocytes indicated that increased SERCA expression or increased expression of mutant phospholamban transgene led to increased SERCA2 activity, resulting in an increased contractile phenotype. Recent findings by other investigators also indicate that decreased SERCA2 activity can be increased under in vivo conditions using adenoviral vector-based SERCA2 expression. A gene therapy type of approach delivering increased amounts of SERCA or phospholamban mutants leading to increased SERCA activity should therefore be considered in the future.

12/7/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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12168324 BIOSIS NO.: 199900463173
Captopril treatment improves the sarcoplasmic reticular Ca2+ transport in heart failure due to myocardial infarction.
AUTHOR: Shao Qiming; Ren Bin; Zarain-Herzberg Angel; Ganguly Pallab K; Dhalla Naranjan S(a)
AUTHOR ADDRESS: (a)Institute of Cardiovascular Sciences, St Boniface General Hospital Research Centre, 351 Tache Avenue, Winnipeg, MB, R2H 2A6
**Canada
JOURNAL: Journal of Molecular and Cellular Cardiology 31 (9):p1663-1672 Sept., 1999
ISSN: 0022-2828
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Although captopril, an angiotensin-converting enzyme (ACE) inhibitor, has been shown to exert a beneficial effect on cardiac function in heart failure, its effect on the status of sarcoplasmic reticulum (SR) Ca2+ transport in the failing heart has not been examined previously. In order to determine whether captopril has a protective action on cardiac function, as well as cardiac SR Ca2+-pump activity and gene expression, a rat model of heart failure due to myocardial infarction was employed in this study. Sham operated and infarcted rats were given captopril (2 g/l) in drinking water; this treatment was started at either 3 or 21 days and was carried out until 8 weeks after the surgery. The untreated animals with myocardial infarction showed increased heart weight and elevated left ventricular end diastolic pressure, reduced rates of pressure development and pressure fall, as well as depressed SR Ca2+ uptake and Ca2+-stimulated ATPase activities in comparison with the sham control group. These hemodynamic and biochemical
changes in the failing hearts were prevented by treatment of the infarcted animals with captopril. Likewise, the observed reductions in the SR Ca2+ pump and phospholamban protein contents, as well as in the mRNA levels for SR Ca2+ pump ATPase and phospholamban, in the failing heart were attenuated by captopril treatment. These results suggest that heart failure is associated with a defect in the SR Ca2+ handling and a depression in the gene expression of SR proteins; the beneficial effect of captopril in heart failure may be due to its ability to prevent remodeling of the cardiac SR membrane.
? ds

Set Items Description
S1 1736 HEART AND (DISEAS? OR FAILURE?) AND PHOSPHOLAMBAN
S2 927 RD S1 (unique items)
S3 518 S2 AND PY<2000
S4 72 S3 AND (TREAT? OR AMELORIAT?)
S5 265 S3 AND CONTRACT?
S6 225 S5 NOT S4
S7 172 S6 AND CALCIUM
S8 14 S7 AND ATP
S9 873 PHOSPHOLAMBAN AND (ADMINIST? OR TREAT? OR INJECT?)
S10 549 S9 AND PY<2000
S11 512 S10 AND (HEART OR CARDIAC)
S12 336 S11/DE
? s s11 and dt=review
512 S11
2142085 DT=REVIEW
S13 17 S11 AND DT=REVIEW
? t s13/7/all
>>>Format 7 is not valid in file 143

13/7/1 (Item 1 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
(c) 2003 Inst for Sci Info. All rts. reserv.

07143206 Genuine Article#: 127XJ Number of References: 65
Title: Molecular aspects of adrenergic signal transduction in %%%cardiac%%%
failure
Author(s): Hajjar RJ; Muller FU; Schmitz W; Schnabel P; Bohm M (REPRINT)
Corporate Source: UNIV COLOGNE,INNERE MED KLIN 3, JOSEPH STELZMANN STR
9/D-50924 COLOGNE//GERMANY/ (REPRINT); UNIV COLOGNE,INNERE MED KLIN
3/D-50924 COLOGNE//GERMANY/; UNIV MUNSTER,INST PHARMAKOL &
TOXIKOL/D-48149 MUNSTER//GERMANY/; HARVARD UNIV,SCH MED, MASSACHUSETTS
GEN HOSP, CTR CARDIOVASC/CHARLESTOWN//MA/02129
Journal: JOURNAL OF MOLECULAR MEDICINE-JMM, %%%1998%%%, V76, N11 (OCT), P
747-755
ISSN: 0946-2716 Publication date: 19981000
Publisher: SPRINGER VERLAG, 175 FIFTH AVE, NEW YORK, NY 10010
Language: English Document Type: %%%REVIEW%%%
Abstract: Abnormal beta-adrenergic signal transduction and intracellular Ca2+ handling appear to be a major cause of systolic and diastolic dysfunction in humans with %%%heart%%% failure. The precise mechanisms
which cause an alteration in Ca2+ handling have been a subject of investigation in recent years. Several lines of evidence suggest that activation of neurohormonal systems plays a central role. Altered Ca2+-handling (increased diastolic concentrations, reduced systolic Ca2+ release) have a strong impact on diastolic and systolic performance of failing hearts. Sarcoplasmic reticulum Ca2+ ATPase is reduced in activity and in steady-state mRNA concentration. The Na+-Ca2+ exchanger is upregulated at the mRNA and protein levels. %%%Phospholamban%%% depends strongly on cAMP-dependent phosphorylation.
A strong sympathetic activation has been shown to desensitize the cAMP system. At the receptor level, there is downregulation of beta(1)-adrenergic receptors. An uncoupling of beta(2)-adrenoceptors has been attributed to an increased activity and gene expression of beta-adrenergic receptor kinase in failing myocardium, leading to phosphorylation and uncoupling of receptors. Finally, recent evidence suggests that cAMP-dependent transcription mechanisms may play a role during beta-adrenergic stimulation and cardiomyopathy with %%%heart%%%
failure - by means of altered actions of cAMP response element binding protein, the cAMP response element modulator, or the activating transcription factor 1. The exact characterization of signal transduction defects could offer novel approaches to the pharmacological %%%treatment%%% of %%%heart%%% failure.

13/7/2 (Item 2 from file: 34)
DIALOG(R)File 34:SciSearch(R) Cited Ref Sci
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03542982 Genuine Article#: PL355 Number of References: 117
Title: PHYSIOLOGICAL AND PHARMACOLOGICAL FACTORS THAT AFFECT MYOCARDIAL
RELAXATION
Author(s): VITTONE L; MUNDINAWEILENMANN C; MATTIAZZI A; CINGOLANI H
Corporate Source: NATL UNIV LA PLATA,FAC CIENCIAS MED,CTR INVEST
CARDIOVASC,60 & 120/RA-1900 LA PLATA//ARGENTINA/; NATL UNIV LA
PLATA,FAC CIENCIAS MED,CTR INVEST CARDIOVASC/RA-1900 LA PLATA//ARGENTINA/
Journal: JOURNAL OF PHARMACOLOGICAL AND TOXICOLOGICAL METHODS, %%%1994%%%
, V32, N1 (SEP), P7-18
ISSN: 1056-8719
Language: ENGLISH Document Type: %%%REVIEW%%%
Abstract: Evaluation of the myocardial relaxation has become important in the last years. Pm impaired relaxation may precede contractile dysfunctions and even cause %%%heart%%% failure. To %%%treat%%% this
impaired lusitropism it is necessary to properly assess the lusitropic state of the %%%heart%%% and understand how drugs affect the

cellular
mechanisms underlying myocardial relaxation (sarcoplasmic reticulum function, Ca2+ fluxes through the sarcolemma and myofilament Ca2+ sensitivity). Current information regarding these issues is provided in this review. The relative usefulness of the mechanical parameters used to evaluate the lusitropic state of the %%%heart%%% in experimental models applied in pharmacology will also be discussed.

13/7/3 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE

07567161 EMBASE No: 1999032115
Genetically engineered mice: Model systems for left ventricular failure
Kadambi V.J.; Kranias E.G.
Dr. E.G. Kranias, Dept. of Pharmacol./Cell Biophysics, University of Cincinnati, College of Medicine, PO Box 670575, Cincinnati, OH 45267-0575
United States
Journal of Cardiac Failure (J. CARD. FAIL.) (United States) 1998, 4/4 (349-361)
CODEN: JCFAF ISSN: 1071-9164
DOCUMENT TYPE: Journal; %%%Review%%%
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 59

The advent of mouse genetic manipulation coupled with the development of miniaturized technology to characterize the obtained phenotypes have provided significant insights into the genetic mechanisms underlying cardiovascular function in health and disease. It is now obvious that alterations of the expression (decreased or increased) levels or function of a single gene, as outlined in this review, may result in %%%cardiac%%% hypertrophy and/or failure. Thus, a number of '%%%heart%%% failure candidate genes' have been identified. However, characterization of their corresponding mouse phenotypes has indicated that there is a compensatory 'cross-talk' between a specific 'candidate gene' and various other genes, resulting in altered expression of multiple gene products, which may mask or contribute to the observed %%%heart%%% failure phenotype. Further studies using new advances in transgenic mouse technology, which allow for tissue-specific ablation or tissue-specific inducible expression of targeted gene products along with introduction of specific mutations in the gene of interest, hold promise for identifying a single or a cluster of 'candidate genes' for %%%heart%%% failure. Nevertheless, the rapid development and characterization of the various mouse models described in this article have provided meaningful new information on the molecular mechanisms underlying %%%cardiac%%% function and dysfunction. Furthermore,
these models have lent valuable insights into genetic targets for %%%treatment%%% of %%%heart%%% disease. As noted earlier, overexpression of
the beta2-adrenergic receptor or its kinase inhibitor, overexpression of SR Casup 2sup +-ATPase, or downregulation of %%%phospholamban%%% expression
may each result in improved contractility and this may be beneficial for the %%%treatment%%% of the failing %%%heart%%%. In addition, the involvement of the calcineurin pathway in the cause/progression of %%%heart%%% disease will undoubtedly open new and unique avenues in the %%%treatment%%% of %%%heart%%% failure. Thus, it is expected that further
studies using genetically engineered mouse models will not only continue to advance our understanding of the genetic regulation of %%%cardiac%%% function and dysfunction, but will also provide valuable insights into the development of therapeutic approaches to %%%treat%%% %%%heart%%% failure.

13/7/4 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE

07433549 EMBASE No: 1998350357
Molecular aspects of adrenergic signal transduction in %%%cardiac%%% failure
Hajjar R.J.; Muller F.U.; Schmitz W.; Schnabel P.; Bohm M.
M. Bohm, Universitat Koln, Klinik III fur Innere Medizin, Joseph-Stelzmann-Strasse 9, D-50924 Cologne Germany
Journal of Molecular Medicine (J. MOL. MED.) (Germany) 1998, 76/11 (747-755)
CODEN: JMLME ISSN: 0946-2716
DOCUMENT TYPE: Journal; %%%Review%%%
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 65

Abnormal beta-adrenergic signal transduction and intracellular Casup 2sup + handling appear to be a major cause of systolic and diastolic dysfunction in humans with %%%heart%%% failure. The precise mechanisms which cause an
alteration in Casup 2sup + handling have been a subject of investigation in recent years. Several lines of evidence suggest that activation of neurohormonal systems plays a central role. Altered Casup 2sup +-handling (increased diastolic concentrations, reduced systolic Casup 2sup + release) have a strong impact on diastolic and systolic performance of failing hearts. Sarcoplasmic reticulum Casup 2sup + ATPase is reduced in activity and in steady-state mRNA concentration. The Nasup +sup -Casup 2sup + exchanger is upregulated at the mRNA and protein levels. %%%Phospholamban%%% depends strongly on cAMP-dependent phosphorylation. A
strong sympathetic activation has been shown to desensitize the cAMP system. At the receptor level, there is downregulation of betainf 1-adrenergic receptors. An uncoupling of betainf 2-adrenoceptors has been attributed to an increased activity and gene expression of beta-adrenergic receptor kinase in failing myocardium, leading to phosphorylation and uncoupling of receptors. Finally, recent evidence suggests that cAMP-dependent transcription mechanisms may play a role during beta-adrenergic stimulation and cardiomyopathy with %%%heart%%% failure -
by means of altered actions of cAMP response element binding protein, the cAMP response element modulator, or the activating transcription factor 1. The exact characterization of signal transduction defects could offer novel approaches to the pharmacological %%%treatment%%% of %%%heart%%% failure.

13/7/5 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE

05741474 EMBASE No: 1994158897
Pharmacology of loprinone (E-1020), a new pyridinone inodilator, as a therapeutic agent for acute %%%heart%%% failure
Endoh M.
Department of Pharmacology, Yamagata Univ School of Medicine,Yamagata 990-23 Japan
Cardiovascular Drug Reviews (CARDIOVASC. DRUG REV.) (United States) 1993, 11/4 (432-450)
CODEN: CDREE ISSN: 0897-5957
DOCUMENT TYPE: Journal; %%%Review%%%
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Intracellular signal transduction processes of the regulation of myocardial contractility mediated by cyclic AMP has been established fairly well. It became evident that the cAMP-mediated regulations of functional proteins such as L-type calcium channels, SR protein %%%phospholamban%%%,
and troponin I are different quantitatively and qualitatively depending on the agents that affect the process of cAMP metabolism. Selective PDE III inhibitors and betainf 1-adrenoceptor partial agonists increase myocardial contractility with accumulation of cAMP less than that produced by nonselective PDE inhibitors and beta-receptor full agonists. These new cardiotonic agents may have definite advantages in respect to the incidence of adverse effects such as arrhythmias and myocardial cell death elicited by excessive accumulation of cAMP. These agents produce vasodilation also through accumulation of cAMP in vascular smooth muscle, and are, therefore,
called inodilators. A new cardiotonic, loprinone, belongs to such a class of new agents. It has been shown that loprinone is effective in improving hemodynamic state in patients with acute %%%heart%%% failure.

13/7/6 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE

05570985 EMBASE No: 1993339085
Left ventricular diastolic function in the normal and diseased %%%heart%%%: Perspectives for the anesthesiologist (second of two parts)
Pagel P.S.; Grossman W.; Haering J.M.; Warltier D.C.
Medical College of Wisconsin, MFRC, 8701 Watertown Plank Road,Milwaukee,
WI 53226 United States
Anesthesiology (ANESTHESIOLOGY) (United States) 1993, 79/5 (1104-1120)
CODEN: ANESA ISSN: 0003-3022
DOCUMENT TYPE: Journal; %%%Review%%%
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Several important questions remain to be answered by future research. First, it is unclear whether any abnormal index of diastolic function can be used to estimate disease severity, or to prognostically identify patients who will subsequently develop systolic abnormalities or frank left ventricular dysfunction. A temporal relationship between the appearance of diastolic dysfunction and ultimate left ventricular decompensation may, theoretically, exist, but such a relationship has yet to be established. Second, a growing body of evidence indicates that pharmacologic therapy with Casup 2sup + channel antagonists, beta-adrenergic agonists or antagonists, phosphodiesterase inhibitors, or angiotensin converting enzyme inhibitors may acutely or chronically benefit certain patients with diastolic dysfunction. Whether the impact of early recognition and therapeutic intervention in patients with diastolic dysfunction can be translated into an improvement of quality of life or enhanced survival remains unknown. Third, recent evidence indicates that fundamental changes in the biochemistry of the %%%cardiac%%% myocyte may represent a final common pathway for the development of congestive %%%heart%%% failure resulting from intrinsic %%%cardiac%%% disease. Altered expression of genes
coding for the ATP-dependent Casup 2sup + pumps in the sarcolemma and the
sarcoplasmic reticulum, regulatory proteins such as %%%phospholamban%%%,
and the proteins composing the contractile apparatus have been identified that play critical roles in the pathophysiology of myocardial failure, and have important implications for potential pharmacologic therapy. Future research will more clearly elucidate these cellular and biochemical mechanisms of left ventricular failure. Lastly, although intravenous and inhalational anesthetics produce derangements in normal diastolic function to varying degrees, whether the effects of these agents on diastolic performance are exacerbated in disease processes manifested by abnormal diastolic mechanics requires further evaluation.

13/7/7 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11669835 99104928 PMID: 9887981
The role of %%%phospholamban%%% and SERCA3 in regulation of smooth
muscle-endothelial cell signalling mechanisms: evidence from gene-ablated mice.
Paul R J
Department of Molecular and Cellular Physiology, University of Cincinnati College of Medicine, OH 45267-0576, USA.
Acta physiologica Scandinavica (ENGLAND) Dec %%%1998%%%, 164 (4)
p589-97, ISSN 0001-6772 Journal Code: 0370362
Contract/Grant No.: HL54829; HL; NHLBI
Document type: Journal Article; %%%Review%%%; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
It is generally agreed that intracellular Ca2+ stores, the sarco(endo)plasmic-reticulum (SER), affect Ca2+ homeostasis and thus contractility of vascular smooth muscle. There is, however, no general consensus as to the magnitude of the SER contribution to Ca2+ handling, the basis for isoforms of the SER Ca(2+)-ATPases (SERCAs) or the role of an SER-associated regulatory protein, %%%phospholamban%%% (PLB). Although the biochemical and cell biological roles of the SER have been intensely studied in vitro, the development of gene-targeted and transgenic mouse models enables one to extend our information to the in vivo levels. A brief review of the role of PLB and SERCA function in vascular and endothelial cell function is presented. Studies on the PLB gene-ablated mouse indicate that vascular contractility is considerably altered. This is mirrored by changes in intracellular Ca2+. Moreover, differences in contractility of the gene-ablated tissues are eliminated by %%%treatment%%% with cyclopiazonic acid, which pharmacologically abolishes SER function by inhibiting the Ca(2+)-ATPase. Thus PLB modulation of sarcoplasmic reticulum (SR) Ca2+ uptake plays a major role in modulating vascular contractility. It is interesting that endothelium-dependent relaxation was decreased in the PLB-deficient aorta. This is surprising in light of the PLB distribution, thought to be limited to %%%cardiac%%%, slow skeletal and smooth muscle. Our data indicate the presence of PLB in endothelial cells and point to an unrecognized pathway for modulation of endothelial cell [Ca2+]i and vascular contractility. Data from smooth muscle tissues of the SERCA3 gene-ablated mouse demonstrate that this isoform affects endothelium-dependent function, but not that of smooth muscle, consistent with its known distribution. This isoform appears to perform a modulatory function, rather than the more essential role of SERCA2. Gene-targeted and
transgenic models provide an important avenue for understanding the role of SER in vascular signalling. (54 Refs.)
Record Date Created: 19990407
Record Date Completed: 19990407

13/7/8 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11608687 99041492 PMID: 9826119
Molecular aspects of adrenergic signal transduction in %%%cardiac%%% failure.
Hajjar R J; Muller F U; Schmitz W; Schnabel P; Bohm M
Harvard Medical School, Massachusetts General Hospital, Cardiovascular Center, Charlestown 02129-2060, USA.
Journal of molecular medicine (Berlin, Germany) (GERMANY) Oct %%%1998%%%, 76 (11) p747-55, ISSN 0946-2716 Journal Code: 9504370
Document type: Journal Article; %%%Review%%%; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Abnormal beta-adrenergic signal transduction and intracellular Ca2+ handling appear to be a major cause of systolic and diastolic dysfunction in humans with %%%heart%%% failure. The precise mechanisms which cause an
alteration in Ca2+ handling have been a subject of investigation in recent years. Several lines of evidence suggest that activation of neurohormonal systems plays a central role. Altered Ca2+-handling (increased diastolic concentrations, reduced systolic Ca2+ release) have a strong impact on diastolic and systolic performance of failing hearts. Sarcoplasmic reticulum Ca2+ ATPase is reduced in activity and in steady-state mRNA concentration. The Na+-Ca2+ exchanger is upregulated at the mRNA and
protein levels. %%%Phospholamban%%% depends strongly on cAMP-dependent
phosphorylation. A strong sympathetic activation has been shown to desensitize the cAMP system. At the receptor level, there is downregulation of beta1-adrenergic receptors. An uncoupling of beta2-adrenoceptors has been attributed to an increased activity and gene expression of beta-adrenergic receptor kinase in failing myocardium, leading to phosphorylation and uncoupling of receptors. Finally, recent evidence suggests that cAMP-dependent transcription mechanisms may play a role during beta-adrenergic stimulation and cardiomyopathy with %%%heart%%%
failure - by means of altered actions of cAMP response element binding protein, the cAMP response element modulator, or the activating transcription factor 1. The exact characterization of signal transduction defects could offer novel approaches to the pharmacological %%%treatment%%%
of %%%heart%%% failure. (65 Refs.)
Record Date Created: 19990125
Record Date Completed: 19990125

13/7/9 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10513262 96323886 PMID: 8739255
Adrenergic and muscarinic receptor regulation and therapeutic implications in %%%heart%%% failure.
Schmitz W; Boknik P; Linck B; Muller F U
Institut fur Pharmakologie und Toxikologie, Westfalische Wilhelms-Universitat, Munster, Germany.
Molecular and cellular biochemistry (NETHERLANDS) Apr 12-26 %%%1996%%%,
157 (1-2) p251-8, ISSN 0300-8177 Journal Code: 0364456
Document type: Journal Article; %%%Review%%%; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In end-stage %%%heart%%% failure the expression of different myocardial
regulatory proteins involved in the beta-adrenergic cAMP signalling pathway is altered. The downregulation of beta 1-adrenoceptors and their uncoupling from the effector as well as an increased expression of the inhibitory GTP-binding protein seem to be the most important alterations. Since catecholamine levels are elevated in these patients and since some alterations can be 'restored' after %%%treatment%%% with beta-adrenoceptor
antagonists it was hypothesized that excessive beta-adrenergic stimulation could be involved in these alterations. In this article the changes of beta-adrenergic receptors, GTP-binding proteins, sarcoplasmic reticulum Ca(2+)-ATPase and of %%%phospholamban%%% found in %%%heart%%% failure are
addressed with its possible therapeutic implications. (91 Refs.)
Record Date Created: 19961017
Record Date Completed: 19961017

13/7/10 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10337514 96139844 PMID: 8569720
Regulation of %%%phospholamban%%% and troponin-I phosphorylation in the
intact rat cardiomyocytes by adrenergic and cholinergic stimuli: roles of cyclic nucleotides, calcium, protein kinases and phosphatases and depolarization.
Sulakhe P V; Vo X T
Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Canada.
Molecular and cellular biochemistry (NETHERLANDS) Aug-Sep %%%1995%%%,
149-150 p103-26, ISSN 0300-8177 Journal Code: 0364456
Document type: Journal Article; %%%Review%%%; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Protein phosphorylation was investigated in [32P]-labeled cardiomyocytes isolated from adult rat %%%heart%%% ventricles. The beta-adrenergic
stimulation (by isoproterenol, ISO) increased the phosphorylation of inhibitory subunit of troponin (TN-I), C-protein and %%%phospholamban%%%
(PLN). Such stimulation was largely mediated by increased adenylyl cyclase (AC) activity, increased myoplasmic cyclic AMP and increased cyclic AMP dependent protein kinase (A-kinase)-catalyzed phosphorylation of these proteins in view of the following observations: (a) dibutyryl-and bromo-derivatives of cyclic AMP mimicked the stimulatory effect of ISO on
protein phosphorylation while (b) Rp-cyclic AMP was found to attenuate ISO-dependent stimulation. Unexpectedly, 8-bromo cyclic GMP was found to
markedly increase TN-I and PLN phosphorylation. Both beta 1- and beta 2-adrenoceptors were present and ISO binding to either receptor was found
to stimulate myocyte AC. However, the stimulation of the beta 2-AR only marginally increased while the stimulation of beta 1-AR markedly increased PLN phosphorylation. Other stimuli that increase tissue cyclic AMP levels also increased PLN and TN-I phosphorylation and these included isobutylmethylxanthine (non-specific phosphodiesterase inhibitor), milrinone (inhibits cardiotonic inhibitable phosphodiesterase, sometimes called type III or IV) and forskolin (which directly stimulates adenylyl cyclase). Cholinergic agonists acting on cardiomyocyte M2-muscarinic receptors that are coupled to AC via pertussis toxin(PT)-sensitive G proteins inhibited AC and attenuated ISO-dependent increases in PLN and TN-I phosphorylation. The in vivo PT %%%treatment%%%, which ADP-ribosylated
Gi-like protein(s) in the myocytes, markedly attenuated muscarinic inhibitory effect on PLN and TN-I phosphorylation on one hand and, increased the beta-adrenergic stimulation, on the other. Controlled exposure of isolated myocytes to N-ethyl maleimide, also led to the findings similar to those seen following the PT %%%treatment%%%. Exposure
of myocytes to phorbol, 12-myristate, 13-acetate (PMA) increased the protein phosphorylation, augmenting the stimulation by ISO, and such augmentation was antagonized by propranolol suggesting modulation of the beta-adrenoceptor coupled AC pathway by PMA. Okadaic acid (OA) exposure of
myocytes also increased protein phosphorylation with the results supporting the roles for type 1 and 2A protein phosphatases in the dephosphorylation of PLN and TN-I. Interestingly OA %%%treatment%%% attenuated the muscarinic
inhibitory effect which was restored by subsequent brief exposure of myocytes to PMA. While the stimulation of alpha adrenoceptors exerted little effect on the phosphorylation of PLN and TN-I, inactivation of alpha adrenoceptors by chloroethylclonidine (CEC), augmented beta-adrenergically stimulated phosphorylation. KCl-dependent depolarization of myocytes was observed to potentiate ISO-dependent increase in phosphorylation (incubation period 15 sec to 1 min) as well as to accelerate the time-dependent decline in this phosphorylation seen upon longer incubation. Verapamil decreased ISO-stimulated protein phosphorylation in the depolarized myocytes. Depolarization was found to have little effect on the muscarinic inhibitory action on phosphorylation. Prior %%%treatment%%% of
myocytes with PMA, was found to augment ISO-stimulated protein phosphorylation in the depolarized myocytes. Such augmented increases were
completely blocked by propranolol. Forskolin also stimulated PLN and TN-I phosphorylation. Prior exposure of myocytes to forskolin followed by incubation in the depolarized and polarized media showed that PLN was dephosphorylated more rapidly in the depolarized myocytes. The results support the view that both cyclic AMP and calcium signals cooperatively increase the rates of phosphorylation of TN-I and PLN in the depolarized cardiomyocytes during beta-adrenergic stimulation. (ABSTRACT TRUNCATED) (
96 Refs.)
Record Date Created: 19960307
Record Date Completed: 19960307

13/7/11 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08924316 20212633 PMID: 10750595
Calcium regulatory proteins and their alteration by transgenic approaches.
Dillmann W H
Department of Medicine, University of California San Diego, La Jolla 92093-0618, USA.
American journal of cardiology (UNITED STATES) Jun 17 %%%1999%%%, 83
(12A) p89H-91H, ISSN 0002-9149 Journal Code: 0207277
Document type: Journal Article; %%%Review%%%; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Abnormalities in calcium flux have been linked to abnormal contractile behavior of the %%%heart%%% in patients with congestive %%%heart%%% failure
as well as in animal models. Decreased activity or levels of the calcium adenosine triphosphatase of the sarco(endo)plasmic reticulum (SERCA2)

also
presented. (51 Refs.)
Record Date Created: 19890926
Record Date Completed: 19890926

13/7/14 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2003 The Dialog Corp. All rts. reserv.

02197697 76153441 PMID: 176697
Regulation of calcium transport in %%%cardiac%%% sarcoplasmic reticulum
by cyclic AMP-dependent protein kinase.
Tada M; Kirchberger M A; Katz A M
Recent advances in studies on cardiac structure and metabolism (UNITED
STATES) %%%1976%%%, 9 p225-39, ISSN 0363-5872 Journal Code: 0325677
Document type: Journal Article; %%%Review%%%
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A manyfold increase in phosphorylation of %%%cardiac%%% sarcoplasmic
reticulum (SR) was seen when SR was incubated in the presence of a bovine
%%%cardiac%%% cyclic AMP-dependent protein kinase and cyclic AMP. This
phosphoprotein had stability characteristics of a phosphoester in which the
phosphate is incorporated largely into serine, and its formation did not
required calcium ions, unlike the formation of acyl phosphoprotein
intermediate of calcium-transport ATPase which is present within the same
membrane. When examined by sodium dodecyl sulfate-polyacrylamide gel
electrophoresis, the protein kinase-catalyzed phosphorylation occurred at a
22,000-dalton component of the %%%cardiac%%% sarcoplasmic reticulum. This
22,000-dalton protein has been named "%%%phospholamban%%%" (lambda alpha mu
beta alpha nu epsilon iota nu = to receive), based on its ability to
receive phosphate from ATP. Phosphorylation of %%%phospholamban%%% by
cyclic AMP-dependent protein kinase was associated with the stimulation of
calcium transport by the %%%cardiac%%% sarcoplasmic reticulum. This
stimulation was accompanied by an increase in the calcium-activated ATPase
activity, indicating that the overall rate of calcium transport rather than
its efficiency is enhanced by protein kinase. The 22,000-dalton
phopholamban was susceptible to trypsin. Brief digestion with trypsin in
the presence of 1 M sucrose prevented subsequent phosphorylation of
%%%phospholamban%%% , while leaving the calcium pump apparently intact.
Incubation of trypsin-%%%treated%%% sarcoplasmic reticulum with cyclic
AMP-depentent protein kinase did not result in the stimulation of calcium
transport. These results may suggest that %%%phospholamban%%% is a
modulator of the calcium pump of the %%%cardiac%%% sarcoplasmic reticulum.
(48 Refs.)
Record Date Created: 19760602
Record Date Completed: 19760602

13/7/15 (Item 1 from file: 156)
DIALOG(R)File 156:ToxFile
(c) format only 2003 The Dialog Corporation. All rts. reserv.

01107912 96139844 NLM Doc No: 8569720
Regulation of %%%phospholamban%%% and troponin-I phosphorylation in the
intact rat cardiomyocytes by adrenergic and cholinergic stimuli: roles of
cyclic nucleotides, calcium, protein kinases and phosphatases and
depolarization.
Sulakhe P V; Vo X T
Department of Physiology, College of Medicine, University of Saskatchewan, Saskatoon, Canada.
Journal Name: Molecular and cellular biochemistry (NETHERLANDS)
Pub. Year: Aug-Sep %%%1995%%% 149-150 p103-26, ISSN: 0300-8177
Journal Code: 0364456
Document type: Journal Article; %%%Review%%%; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Protein phosphorylation was investigated in [32P]-labeled cardiomyocytes
isolated from adult rat %%%heart%%% ventricles. The beta-adrenergic
stimulation (by isoproterenol, ISO) increased the phosphorylation of
inhibitory subunit of troponin (TN-I), C-protein and %%%phospholamban%%%
(PLN). Such stimulation was largely mediated by increased adenylyl cyclase
(AC) activity, increased myoplasmic cyclic AMP and increased cyclic AMP
dependent protein kinase (A-kinase)-catalyzed phosphorylation of these
proteins in view of the following observations: (a) dibutyryl-and
bromo-derivatives of cyclic AMP mimicked the stimulatory effect of ISO on
protein phosphorylation while (b) Rp-cyclic AMP was found to attenuate
ISO-dependent stimulation. Unexpectedly, 8-bromo cyclic GMP was found to
markedly increase TN-I and PLN phosphorylation. Both beta 1- and beta
2-adrenoceptors were present and ISO binding to either receptor was found
to stimulate myocyte AC. However, the stimulation of the beta 2-AR only
marginally increased while the stimulation of beta 1-AR markedly increased
PLN phosphorylation. Other stimuli that increase tissue cyclic AMP levels
also increased PLN and TN-I phosphorylation and these included
isobutylmethylxanthine (non-specific phosphodiesterase inhibitor),
milrinone (inhibits cardiotonic inhibitable phosphodiesterase, sometimes
called type III or IV) and forskolin (which directly stimulates adenylyl
cyclase). Cholinergic agonists acting on cardiomyocyte M2-muscarinic
receptors that are coupled to AC via pertussis toxin(PT)-sensitive G
proteins inhibited AC and attenuated ISO-dependent increases in PLN and
TN-I phosphorylation. The in vivo PT %%%treatment%%%, which ADP-ribosylated
Gi-like protein(s) in the myocytes, markedly attenuated muscarinic
inhibitory effect on PLN and TN-I phosphorylation on one hand and,
increased the beta-adrenergic stimulation, on the other. Controlled
exposure of isolated myocytes to N-ethyl maleimide, also led to the
findings similar to those seen following the PT %%%treatment%%%. Exposure
of myocytes to phorbol, 12-myristate, 13-acetate (PMA) increased the
protein phosphorylation, augmenting the stimulation by ISO, and such
augmentation was antagonized by propranolol suggesting modulation of the
beta-adrenoceptor coupled AC pathway by PMA. Okadaic acid (OA) exposure of
myocytes also increased protein phosphorylation with the results supporting
the roles for type 1 and 2A protein phosphatases in the dephosphorylation
of PLN and TN-I. Interestingly OA %%%treatment%%% attenuated the muscarinic
inhibitory effect which was restored by subsequent brief exposure of
myocytes to PMA. While the stimulation of alpha adrenoceptors exerted
little effect on the phosphorylation of PLN and TN-I, inactivation of alpha
adrenoceptors by chloroethylclonidine (CEC), augmented beta-adrenergically
stimulated phosphorylation. KCl-dependent depolarization of myocytes was
observed to potentiate ISO-dependent increase in phosphorylation
(incubation period 15 sec to 1 min) as well as to accelerate the
time-dependent decline in this phosphorylation seen upon longer incubation.
Verapamil decreased ISO-stimulated protein phosphorylation in the
depolarized myocytes. Depolarization was found to have little effect on the
muscarinic inhibitory action on phosphorylation. Prior %%%treatment%%% of
myocytes with PMA, was found to augment ISO-stimulated protein
phosphorylation in the depolarized myocytes. Such augmented increases were
completely blocked by propranolol. Forskolin also stimulated PLN and TN-I
phosphorylation. Prior exposure of myocytes to forskolin followed by
incubation in the depolarized and polarized media showed that PLN was
dephosphorylated more rapidly in the depolarized myocytes. The results
support the view that both cyclic AMP and calcium signals cooperatively
increase the rates of phosphorylation of TN-I and PLN in the depolarized
cardiomyocytes during beta-adrenergic stimulation. (ABSTRACT TRUNCATED) (

96 Refs.)
Record Date Created: 19960307

13/7/16 (Item 2 from file: 156)
DIALOG(R)File 156:ToxFile
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00773743 89354495 NLM Doc No: 2670238
Calcium sequestration in human platelets: is it stimulated by protein kinase C?
Yoshida K; Nachmias V T
Department of Legal Medicine, Osaka University School of Medicine, Japan.
Journal Name: Cell calcium (SCOTLAND) Pub. Year: Jul %%%1989%%% 10
(5) p299-307, ISSN: 0143-4160 Journal Code: 8006226
Contract/Grant No.: HL-15835; HL; NHLBI
Document type: Journal Article; %%%Review%%%; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Sequestration of calcium into an intracellular storage site is an important mechanism in helping to maintain a low cytoplasmic Ca2+ level in many cells. In platelets, increasing cytoplasmic cAMP lowers the free calcium level in correlation with the phosphorylation of a 22 kD protein. This protein has been thought to enhance uptake of calcium into a platelet membrane bound storage site by activating a calcium-ATPase activity by analogy with %%%phospholamban%%% in %%%cardiac%%% muscle. The evidence for
an analogue of %%%phospholamban%%% in platelets is unclear. A pathway
involving cAMP dependent kinase also seems unlikely to account for the transience of the calcium signal following agonists in platelets, some of which inhibit the cAMP dependent kinase. Here we discuss the issue of whether activation of protein kinase C, which follows agonist action, leads to enhanced calcium sequestration in platelets and if so, what indications there are for a mechanism. The evidence from our experiments with phorbol
myristate acetate %%%treated%%% platelets shows that such an enhancement
can be produced by activating protein kinase C. Phosphorylation studies suggest the involvement of a polypeptide or polypeptides distinct from the 22 kD polypeptide. Further work to test this idea is necessary. A brief overview of research on the role of phosphoproteins in calcium regulation in platelets and comparison with their role in %%%cardiac%%% muscle is also
presented. (51 Refs.)
Record Date Created: 19890926

13/7/17 (Item 1 from file: 434)
DIALOG(R)File 434:SciSearch(R) Cited Ref Sci
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09592842 Genuine Article#: AD991 Number of References: 90
Title: REGULATION OF %%%CARDIAC%%% SARCOPLASMIC-RETICULUM FUNCTION BY
%%%PHOSPHOLAMBAN%%%
Author(s): EDES I; KRANIAS EG
Corporate Source: UNIV CINCINNATI,COLL MED,DEPT PHARMACOL & CELL
BIOPHYS/CINCINNATI//OH/45267
Journal: MEMBRANE BIOCHEMISTRY, %%%1988%%%, V7, N3, P175-192
Language: ENGLISH Document Type: %%%REVIEW%%%
? ds

Set Items Description
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S2 927 RD S1 (unique items)
S3 518 S2 AND PY<2000
S4 72 S3 AND (TREAT? OR AMELORIAT?)
S5 265 S3 AND CONTRACT?
S6 225 S5 NOT S4
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S8 14 S7 AND ATP
S9 873 PHOSPHOLAMBAN AND (ADMINIST? OR TREAT? OR INJECT?)
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